The chemistry of some dihydropyridines and the synthesis of ellipticine derivatives.

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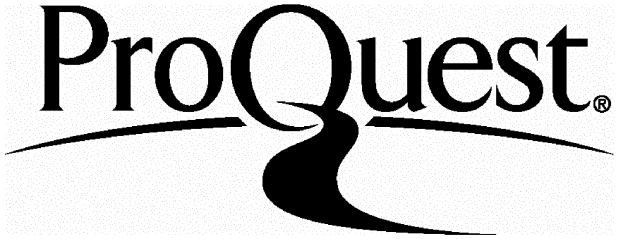
THE CHEMISTRY OF SOME DIHYDROPYRIDINES AND THE SYNTHESIS OF ELLIPTICINE DERIVATIVES

submitted by Michael Driver for the degree

of Ph.D. of the University of Bath 1979



FOR SANDRA

ACKNOWLEDGMENTS

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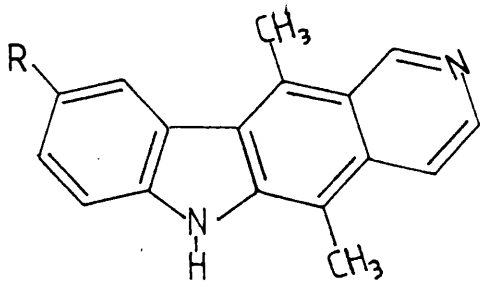
CONTENTS

SUMMARY

A brief summary of the anti-cancer activity of the ellipticines is made together with an indication of the geographical distribution of plants containing ellipticine and related alkaloids. A comprehensive review of the reported synthetic routes to ellipticine and its derivatives is included.

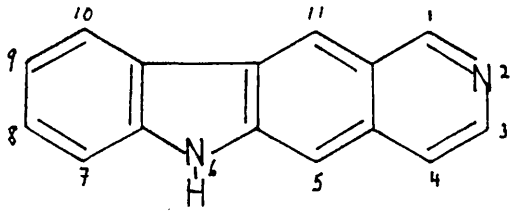
During the course of investigations of one route to the tetracyclic system several new dihydropyridines have been isolated and identified. Modification of this route has led to the preparation of several, previously unreported, ellipticine derivatives while the examination of a new synthetic route has led to the preparation of 5-ethylellipticine. Attempts have been made to adapt this procedure to the preparation of other derivatives.



(1, R=H)
(2, R=MeO)

Table 1

PLANT	ALKALOID	SOURCE	REF.
Ochrosia elliptica, Labill.	Ellipticine 9-Methoxyellipticine Elliptinine Elliptamine Isoreserpiline (Ellep-tine)	New Caledonia Florida(transplanted Australia (-"-) Mascarene Islands	1 92 93 94 95 96
Ochrosia sandwicensis, A.Gray.	Ellipticine 9-Methoxyellipticine 10-Hunterburnine-α-metho-chloride 10-Hydrodydihydrocory-nantheol methochloride N-Methylisoreserpiliniumchloride (Holeinine)	Hawaii	1, 97 98 99
Aspidosperma subincanum, Mart.	N-Methyltetrahydroelli-pticine Ellipticine 3,4-Dihydroellipticine 3,4-Dihydroellipticine-methonitrate Ellipticine methonitrate Olivacine	Peru	100
Ochrosia glomerata, Valeton.	Isoreserpiline Elliptamine Ellipticine Methoxyellipticine	New Guinea	95
Aspidosperma olivaceum, Mull.	Olivacine Uleine	Brazil	101 102
Ochrosia maculata, Jacq.	9-Methoxyellipticine Reserpine Ellipticine	Reunion Island Sri Lanka Mascarene Islands Java, Mauritius	103 104
Ochrosia vitiensis	Ellipticine 9-Methoxyellipticine Isoreserpiline	Fiji	94



INTRODUCTION

Occurrence and Discovery

Ellipticine (1) is a natural product found in plants of the family Apocynaceae. The alkaloid was first isolated in 1959 by Goodwin et al[1] from the leaves of Ochrosia elliptica along with several other compounds including the 9-methoxylated derivative (2). Since its initial discovery in Ochrosia species ellipticine has also been found in plants of several other genera including Peschiera, Aspidosperma and Tabernaemontana frequently accompanied by 9-methoxyellipticine.

Table 1, which lists a number of plants containing ellipticine or related alkaloids, gives an indication of their geographical distribution.

Extracts from many plants containing these alkaloids have been used in the treatment of illness for centuries. Rumphius, for example, in his work "Flora Amboinensis" of 1741 records how the islanders of the Molukian Group used extracts of Ochrosia oppositifolia to treat certain types of nose and face cancers and in the Reunion Islands extracts from the bark of Ochrosia masculata have been used as a tonic and an antianemic.

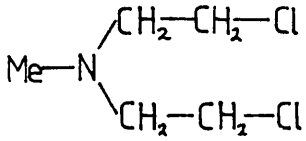
Woodward and his team[2] synthesised the alkaloid during the year of its discovery and this simple, though inefficient route served to prove the structure as that of a substituted 6-H-pyrido-(4, 3-b) carbazole (3). Despite the prompt elucidation of the structure much interest is still generated in ellipticine and its derivatives because of the considerable anti-tumour activity they exhibit.

Cancer and Chemotherapy

Although advances have been made concerning the diagnosis and treatment of cancer it remains a chilling fact that malignant disease causes around one fifth of all the fatalities each year in Great Britain. This constitutes some 110,000 premature deaths of which 30,000 are due to lung cancer and a further 38,000 are due to tumours of the digestive system. In children cancer is the commonest disease causing death, although progress in the treatment of childhood malignancies has been reported recently. In cases of acute lymphoblastic leukemia, for example, dramatic improvements have resulted from the use of more effective combination chemotherapy regimens augmented by radiotherapy in the prophylactic treatment of the central nervous system. This has resulted in 5 year leukemia-free survival rates of over 50% of these being treated[3].

Despite the advances made during recent years it remains true that the more common tumours, such as those of the lung, colon, cervix and stomach are usually insensitive to chemotherapy and thus the treatment of different types of cancer varies considerably. Generally surgery is employed to remove the major manifestations while radiotherapy and chemotherapy are used to "mop up" the remaining traces of the disease. In some cases chemotherapy may be used to cause a rapid shrinkage of the tumour thereby allowing radiotherapy to be used more expeditiously. Complications are many; if the tumour is inaccessible to surgery or if growth is advanced, and if the patient is young or elderly then toxic side-effects may prove a limiting factor or if the malignancy is unresponsive then treatment may not be effective at all.

The efficacy of chemotherapy has increased dramatically with the use of specific drug combinations. The drugs often have



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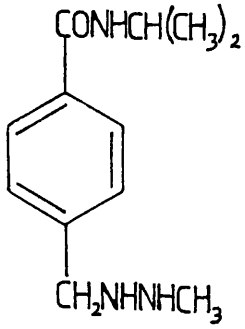

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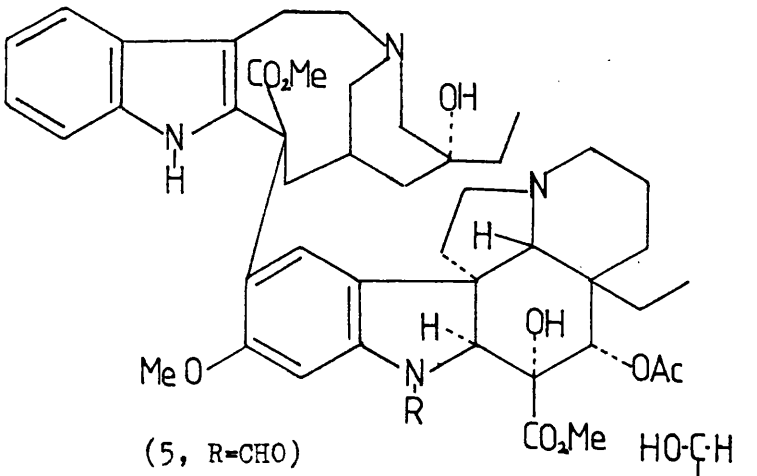
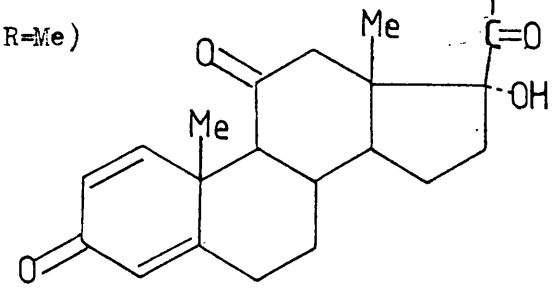


(5, R=CHO)

(9, R=Me)



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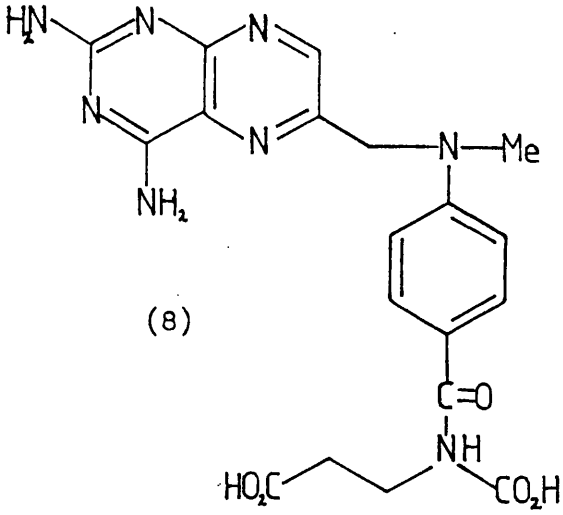

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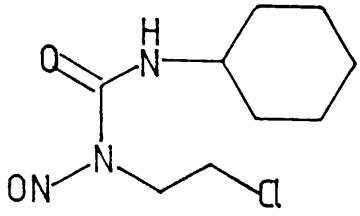


CCNU

TABLE 2

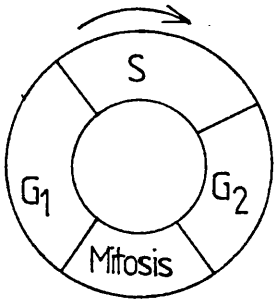
MECHANISM	CLASS	EXAMPLES
Interfere with DNA synthesis.	Pyrimidine analogues Purine analogues Folate antagonists	5-Fluorouracil 6-Mercaptopurine Methotrexate
Interfere with mitotic spindle formation	Vinca alkaloids	Vincristine Vinblastine
Action on transfer RNA	Actinomycin D	Adriamycin
Alkylate and cross-link strands of DNA at any stage of cell growth	Alkylating agents	Mustine hydrochloride Chlorambucil Cyclophosphamide
Bind with DNA and interfere with replication	Antibiotics	Adriamycin Danorubicin
Action unknown	Procarbazine Nitrosoureas	BCNU, CCNU Me CCNU

different mechanisms of action and they provide greater benefit than do the single agents individually. In addition if the side-effects of the drugs are different then they will not be additive and the combination need not be any more toxic. In the treatment of Hodgkin's disease the National Cancer Institute introduced a regimen of 4 drugs (MOPP) comprising mustine (4), vincristine (5), procarbazine (6) and prednisone (7). The use of this combination has led to complete remissions in 80% of patients being treated with over 75% being alive and well after 5 years.

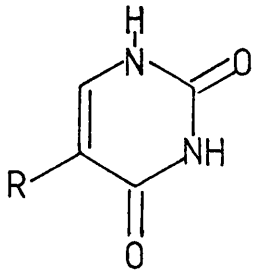
Some of the more important agents which have proved useful in the treatment of human cancer are classified in Table 2.

Nearly all of the cytotoxic drugs in current use act by interfering with cell replication. Some, such as methotrexate (8) and the Vinca alkaloids (5 and 9) are 'phase dependent' and act either during the deoxyribonucleic acid (DNA) synthetic phase (S-phase), of cell growth or during mitosis. Others, including the alkylating agents are 'phase independent' and can affect cells at any stage in the cell cycle (Diagram 1).

Diagram 1

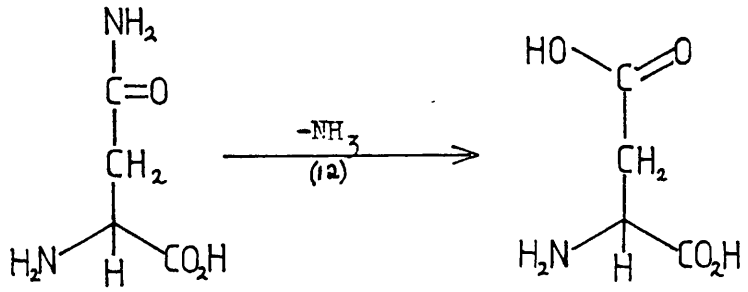


Since the introduction of the concept of the cell cycle it has been recognised that there is an orderly sequence of events, grouped into the four phases of the cell cycle G_1, S, G_2 and M, between the mid-point of mitosis, or division, of a cell and the mid-point of mitosis in one or both daughter cells. Ellipticine is believed to act during the G_1 and M phases although there is some confusion over this point.



(10, R=F)

(11, R=H)



asparagine

aspartic acid

L-asparaginase or L-asparagine amidohydrolase is an enzyme consisting of four subunits with a molecular weight ~130,000. It converts the amino acid asparagine to aspartic acid.

The mechanism of action of any individual drug has normally been determined after its efficacy has been shown, but there are a few examples where a rational approach has led to the development of a new agent. One instance is the use of 5-fluorouracil (10) following the observation that certain tumours preferentially take up uracil (11) compared with normal tissues. More usually anti-cancer agents are discovered by testing on experimental tumours and the activity is quoted as the therapeutic index. This value is a measure of the dose-response relationship and is the ratio of the dose which would prove lethal in 50% of cases to the dose sufficient to prove efficacious in 50% of the cases.

One compound found by testing in this way, L-asparaginase (12), has a therapeutic index value of 7,500, the highest of any agent in any experimental tumour system. This drug was found to be active against several lymphoid malignancies but in practice was disappointing in relation to its promise from experimental work. This is a common occurrence and for this reason clinical evaluation is composed of 3 distinct investigations ;

(1) pharmacological evaluation to determine toxicity

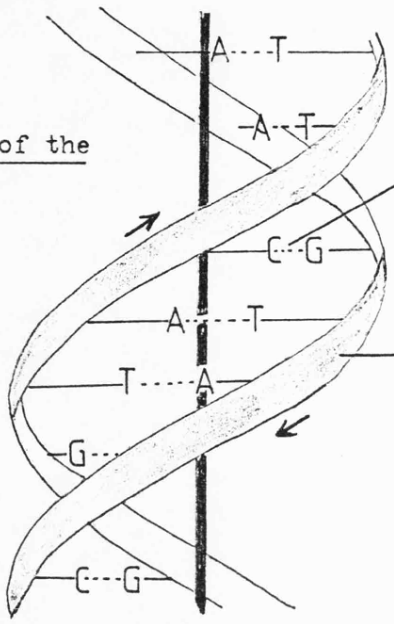
(2) measurement of clinical activity against several tumours

(3) comparative studies to establish the role of the drug in the treatment of a tumour.

Problems are also associated with the way in which the drug is administered and for optimum results the correct presentation must be predetermined.

As stated earlier the majority of anti-cancer drugs used at the present time are cytotoxic agents and these are believed to act preferentially on tumour cells. This apparent selective action on certain tumours depends partly on the paradox that many tumour

Schematic illustration of the double helix

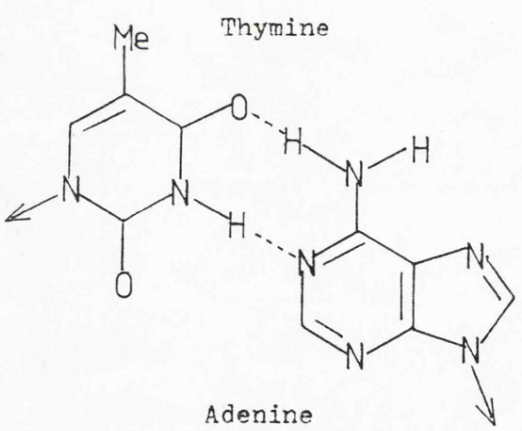


hydrogen bonds between base pairs.

sugar-phosphate backbone

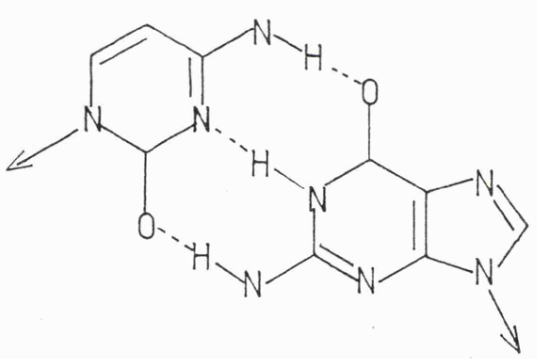
Hydrogen bonding in DNA amino acids

Thymine



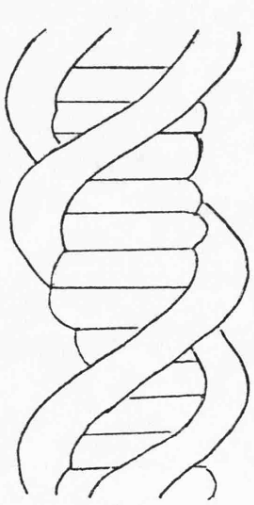
Adenine

Cytosine

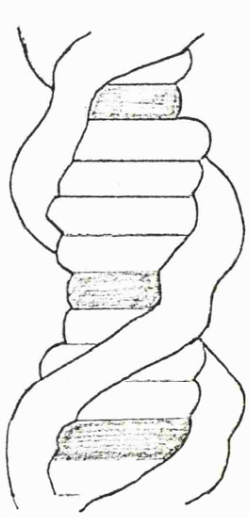


Guanine

Schematic representation of distortion in DNA caused by intercalating substance.



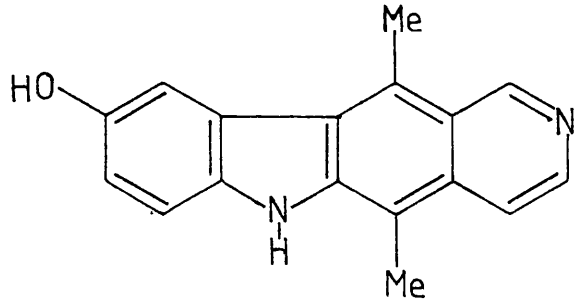
Normal DNA



Distorted DNA

cells proliferate less rapidly than normal tissues and are thus less capable of repairing damage. That some drugs are highly specific has been demonstrated in tests by Skipper et al[6] when results indicated that a cancerous cell could be a million times more sensitive to bis-chlorethylnitrosourea than a normal cell. The basis of this specificity is not generally well understood except in the case of cytotoxic agents which act by intercalation with DNA. In this case the size and shape of the drug is such that it is able to fit into the cavities of the double-coiled helix and bind to adjacent base pairs. This causes a localised distortion of the dynamic structure which is manifested by an unwinding of the helix and this process prevents replication. The specific electronic configuration of a molecule dictates the magnitude of the interaction energy with DNA and along with stereochemical parameters control the ability to intercalate. Planarity or near planarity, appears to be essential for this process and the derivatives of the arc-shaped 6-H-pyrido (4,3-b) carbazoles have most of the required characteristics. Indeed French workers have positively demonstrated that one such derivative 9-methoxyellipticine, intercalates with DNA both at low and high ionic strengths.[7]

Initial pharamacological evaluation of the ellipticines proved disappointing, for in 1967 it was reported that the alkaloid caused respiratory failure in mice.[8] Soon afterwards the outlook improved when it was shown [9,10] that both ellipticine and 9-methoxyelliptine are very active against several test-tumours so that lower dose rates than those used previously might be employed. Particularly encouraging was the activity of the 9-methoxy derivative against the L-1210 III murine leukemia, a neoplasm which is resistent



(13)

to many established anti-cancer drugs. Agents found to be active against this system, which most closely resembles the human situation, have often been found to be effective against cancers in man. During these initial evaluations a relatively broad spectrum of activity was suggested with 9-methoxyellipticine being active against 10 of the 17 mouse tumours tested. It has been since shown that this compound, as the water soluble lactate, has a cytostatic effect on many types of leukemic cells[11] and preclinical trials in dogs showed good tolerance to the drug. Activity against acute myeloblastic leukemia was confirmed in the human clinical screening that followed and out of 12 patients treated 3 complete remissions were reported[12].

A new, highly active anti-tumour agent, 9-hydroxyellipticine (13) was developed as a result of the work of Le Pecq et al[13]. In an attempt to produce a system which allows a rational approach to drug design these workers measured some physiochemical properties of a series of ellipticine derivatives and tried to correlate the results with the anti-cancer activity. They consider that for intercalating drugs high DNA reactivity is a condition necessary for possible anti-tumour activity. The DNA binding constants were determined from the equation below.

$$\log Kap = \log KE^{+} - \log\left[1 + \frac{KH^{-1}}{[H^{+}]} + \log\left(1 + \frac{1}{\alpha}\frac{KH^{-1}}{[H^{+}]}\right)\right]$$

where Kap = DNA binding constant of the derivative

KE^{+} = DNA binding constant of the protonated form

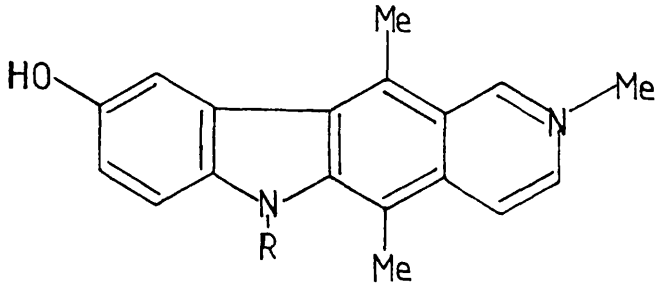
KH^{-1} = dissociation constant of the equilibrium between protonated and non-protonated form of the derivative

and α = the ratio of the DNA binding constants of the protonated and neutral form of the drug.

Table 3

Ellipticine derivative	pK	K_{ap} (pH7.4)	Log K_e^+	Unwinding angle	% cells killed at $\frac{1}{3}LD_{50}$
6-isopentyl	4.7	10^4	6.3	8.8	0
6-isopentylmethoxy	4.5	10^4	6.7	-	-
5,11-didemethyl	6.35	10^4	5.1	-	0
11-demethyl	6.3	2.4×10^4	5.5	-	0
9-methoxy	6.8	10^4	5.7	6.8	90
ellipticine	9.1	1.5×10^4	5.2	9	94
9-bromo	6.1	4.0×10^5	6.9	0*	0
6-methyl	6.1	4.0×10^5	6.9	10.2	92
9-amino	9.8	1.2×10^6	6.1	4	0
9-hydroxy	9.8	2.0×10^6	6.2	12	99.96
9-methoxy-6-methyl	6.45	2.0×10^6	7.3	5	50

* 9-bromoellipticine does not intercalate.



(14, R=H)

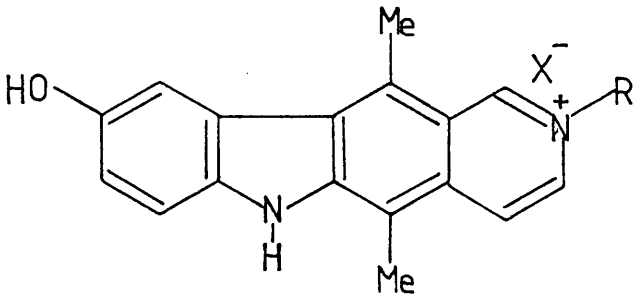
(15, R=Me)

The pharmacological activity was expressed as a percentage of L-1210 cells killed by a dose consisting of $\frac{1}{3}$ of that which would prove lethal to 50% of the animals. The unwinding angle was measured in a number of cases and the results are shown in Table 3.

The D.N.A. binding affinity of the protonated form of the drug is about 30 times larger than that of the neutral form. In solution at physiological pH 7.4 both forms can co-exist and the apparent binding constant measured under these conditions is dependent on the pKa of the molecule. Thus it would appear that the pKa is one of the main factors affecting D.N.A. affinity at this pH.

From the table it is possible to see that there is a partial correlation between the size of the unwinding angle and pharmacological activity. However, since factors such as cell permeability have not been considered it is unrealistic to draw any definite conclusion. It is interesting to note the 3-unit drop in pK and the ten-fold decrease in D.N.A. binding constant when the methyl group in position 11 is replaced by a hydrogen atom. This is most unusual and hard to explain electronically. One possible explanation is that the more bulky methyl substituent affects the planarity and hence the delocalised π-system of the tetracyle.

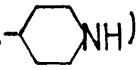
From the results of this study it is apparent that 9-hydroxyellipticine is the most potent of the compounds tested. Skipper *et al*[14] have reported that bis-chlorethylnitrosourea, cyclophosphamide, 6-mercaptopurine and 5-fluoruracil kill 95, 30, 93 and 80% of L-1210 cells whereas under similar conditions 9-hydroxyellipticine kills 99% of cells.[13] Not surprisingly this activity has led to further developments with the 2-methyl and 2, 6-dimethyl analogues (14 and 15) appearing to be even more active. These last two compounds are also more water soluble, an advantage when considering how the drug is to be administered to the patient.



(16, R=CH_2CH_2OH)

(17, R=Et)

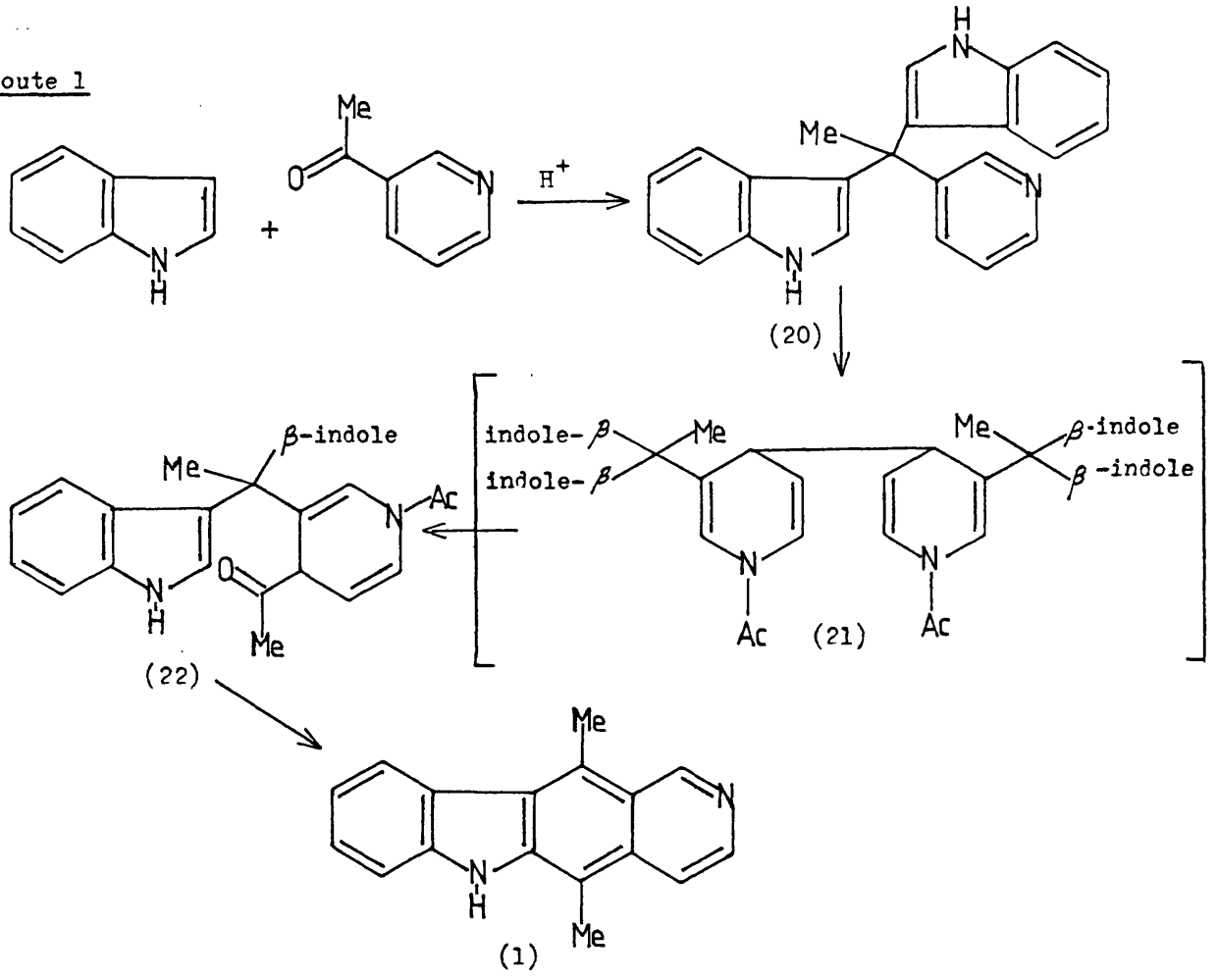
(18, R=$CH_2CH_2N(Et)_2$)

(19, R=CH_2CH_2- )

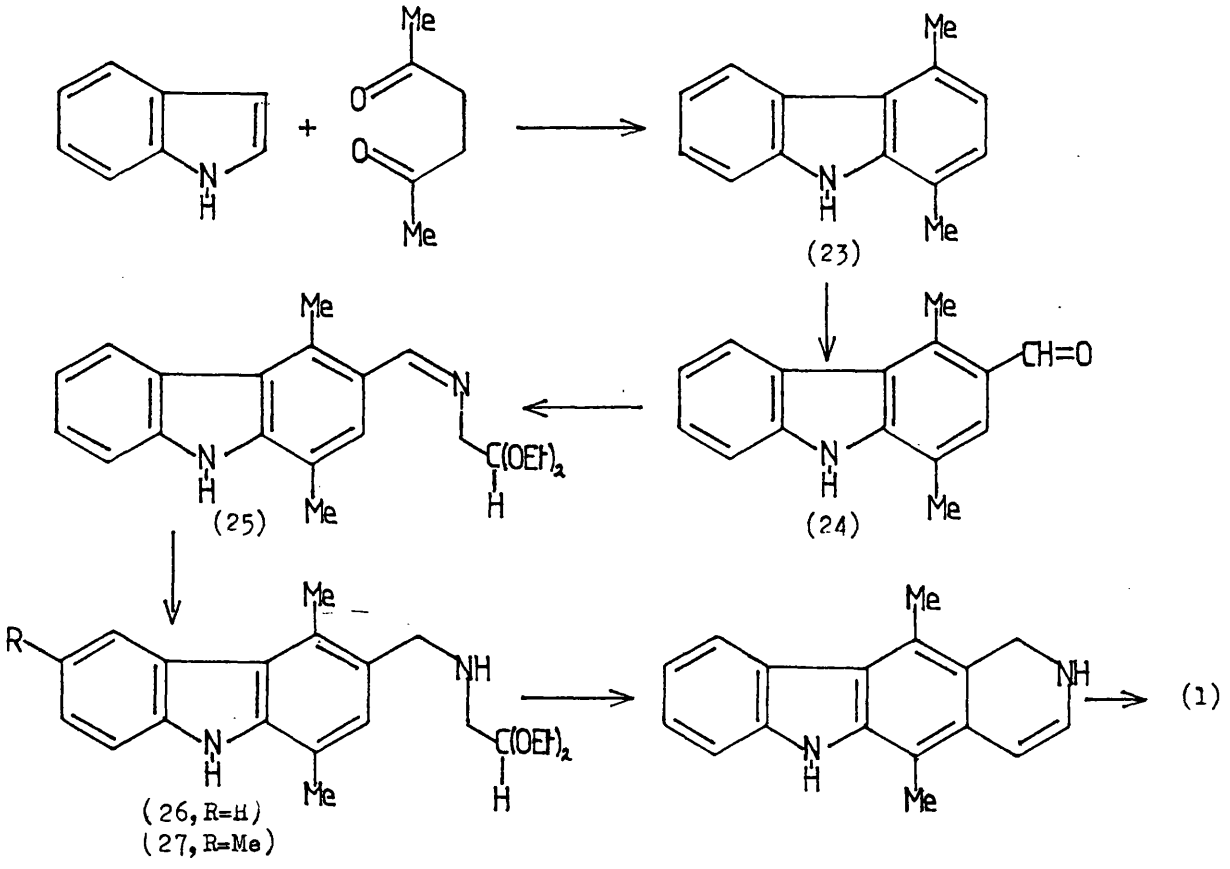
A series of other 2-substituted 9-hydroxyellipticines (16, 17, 18 and 19) prepared recently[15] are currently undergoing biological evaluation.

Considering that relatively few derivatives of the ellipticine group have been submitted for anti-tumour evaluation the range and level of activity so far discovered is remarkable. It is not surprising therefore that so much effort has been put into the development of an efficient sythetic route to the 6-H-pyrido(4,3-b)carbazoles. The published work to date is summarised in the following section.

Route 1



Route 2



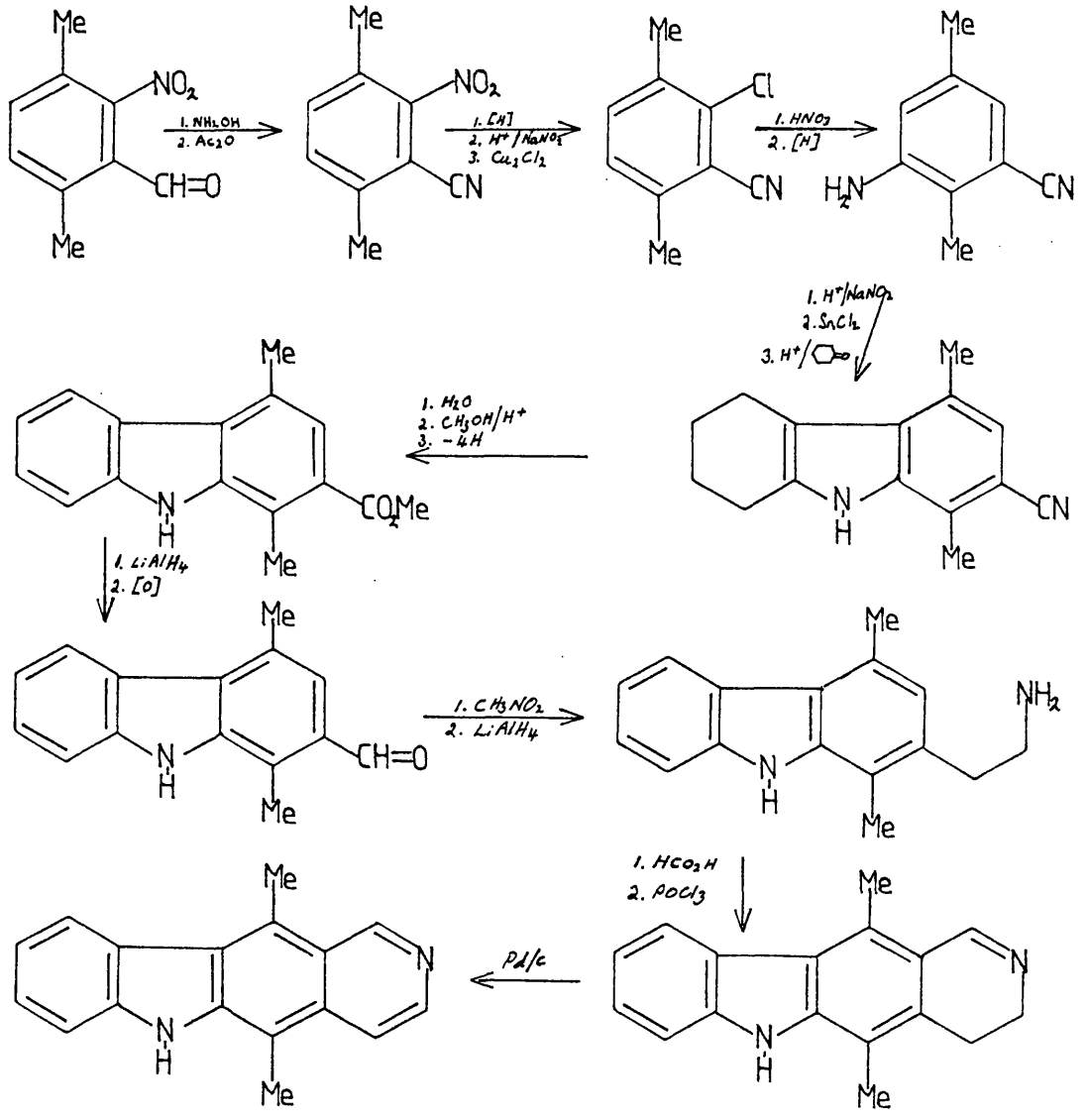
Synthetic efforts towards Ellipticine and its Derivatives

The initial synthesis of the alkaloid by Woodwards' group[2] was remarkable for its direct approach (Route 1) but unfortunately the extremely low overall yield precludes its use as a general practical method. The condensation of indole with 3-acetylpyridine in acetic acid gave 1,1-bis-(3-indolyl)-1-(3-pyridyl) ethane (20) but this '2,1 product' is a poor substrate for the next stage of the synthesis which involves a zinc and acetic acid reductive acetylation procedure. This is presumed to proceed via the dimeric species (21) which disproportionates into starting material and the dihydropyridine (22). This reaction is thus very sensitive to steric factors and although no yield is quoted for this stage it is likely that it was very low. The final oxidative ring-closure is also difficult, requiring the use of sever pyrolytic conditions and perhaps not surprisingly the yield of ellipticine (1) from this final step was only 2%.

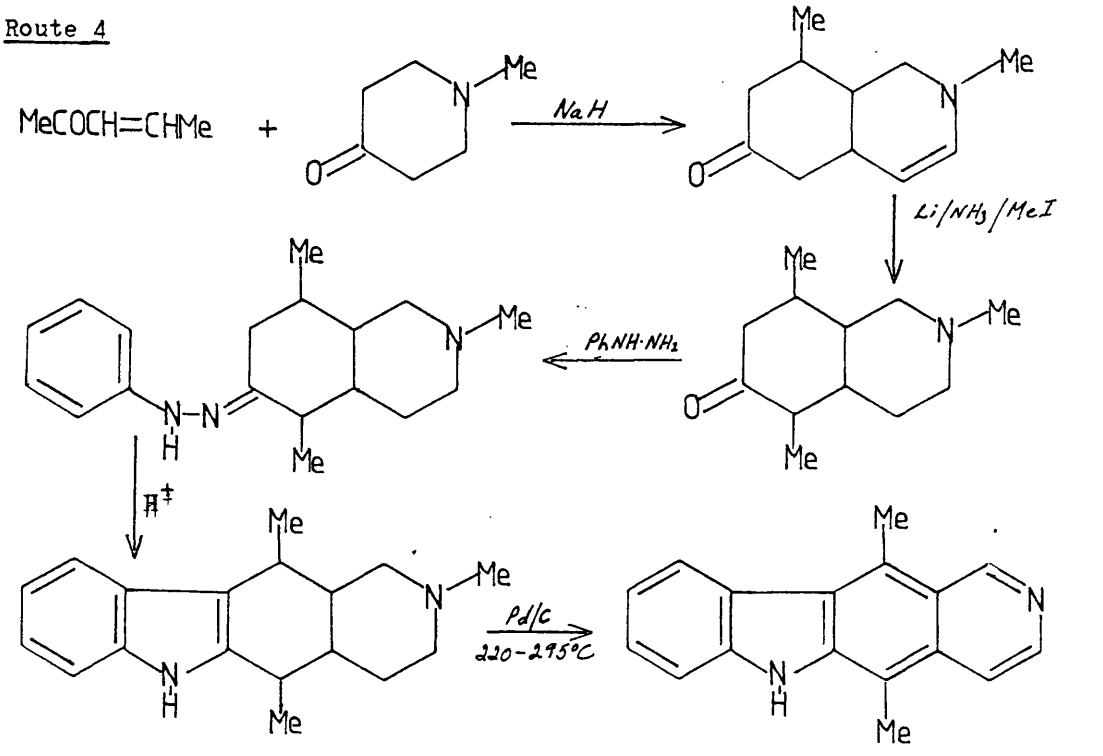
It was another 3 years before a second synthetic effort was reported by Cranwell and Saxton[16], in 1962 (Route 2). They prepared 1,4-dimethylcarbazole (23) in moderate yield by the condensation of indole with hexan-2,5-dione. A Vilsmier formylation gave predominantly the 3-formyl derivative (24) (along with some 3,6-disubstituted product) and this was reacted with 2,2-diethoxyethylamine to give the Schiffs base (25) in good yield. However, attempts to cyclise this compound failed and it was necessary to prepare the dihydro derivative (26) before ring closure could be effected. Subsequent dehydrogenation served to give ellipticine but lowered the overall yield to a disappointing 1.7%.

In following years two more syntheses were reported, the first (Route 3), by Indian workers,[17] was a fine display of

Route 3



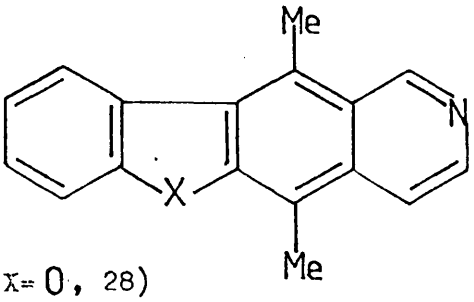
Route 4



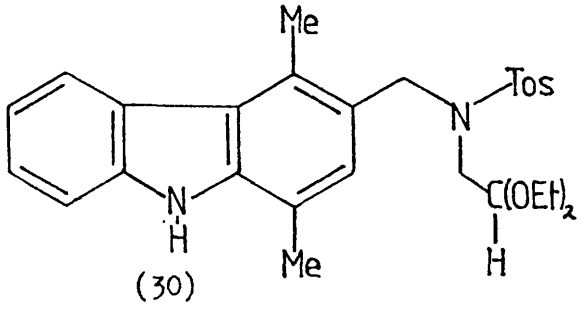
classical organic chemistry techniques but the large number of steps involved in this route are clearly not an advantage in a general preparative procedure although Mosher[18] used a modified sequence to prepare the related alkaloid olivacine. The second synthesis,[19] based upon successful model reactions, involved an approach employing a Fischer-indolisation procedure (Route 4). Unfortunately several steps in the actual synthesis were disappointing, for example the final dehydrogenation worked in only 0.30% yield and again the scheme has no practical value.

In 1967 there came a breakthrough when the potential of Cranwell and Saxton's route was realised by Dalton and co-workers[20]. They discovered that concentrated phosphoric acid effected a Pomeranz-Fritsch cyclisation on the Schiffs base (25) giving ellipticine directly. The concentration of acid was found to be critical and by using 91% phosphoric acid they synthesised 9-methoxyellipticine (2) from the corresponding azomethine (27) in 56% yield. This represented the first synthesis of the alkaloid and served to positively confirm its structure. This direct cyclisation improved the overall yield but it was found that electron-donating substituents in the non-methylated benzenoid ring promoted formylation into sites in addition to the desired 3-position and that electron-withdrawing substituents severely limit the cyclisation reaction. The harsh final conditions precludes the use of this route for the preparation of derivatives containing labile groups but despite these limitations this work represents the first practical route and was used to prepare a number of derivatives[20] including the two related tetracycles (28) and (29)[21].

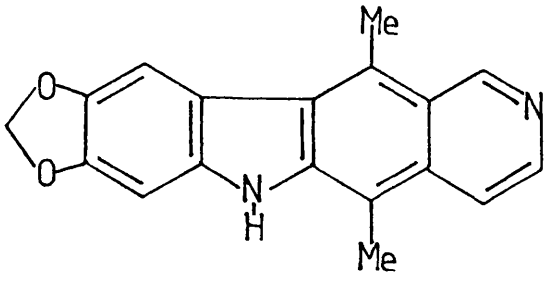
A further improvement of the synthesis was developed in 1975 by Guthrie *et al*[22] when they succeeded in cyclising the



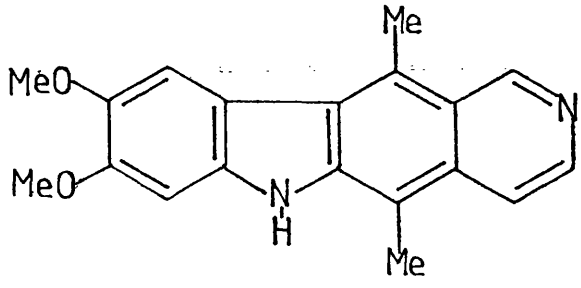
(X= O, 28)
(X= S, 29)



(30)

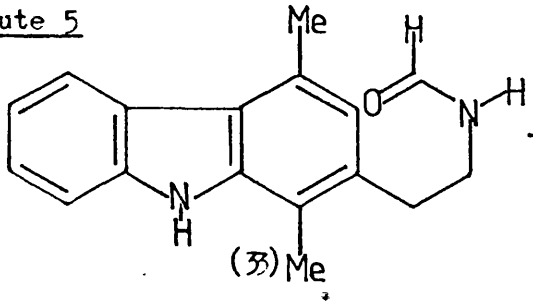


(32)

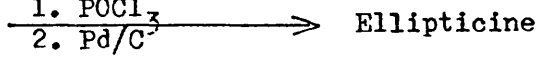


(31)

Route 5

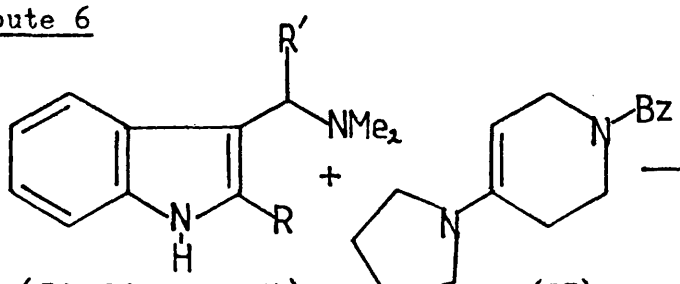


(33)



Ellipticine

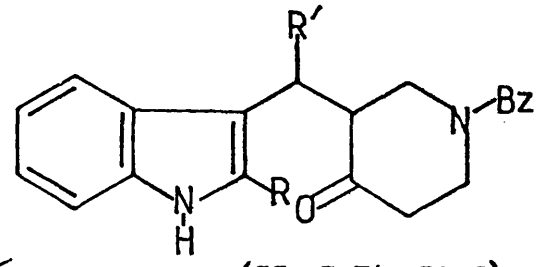
Route 6



(34, R'=Me, R=Et)

(36, R'=Me, R=H)

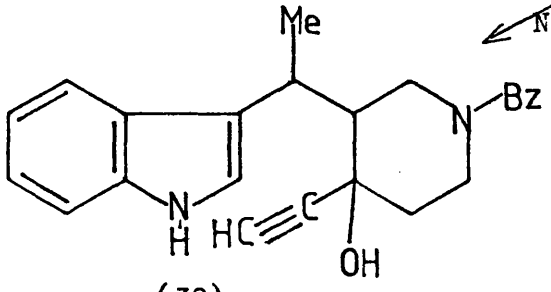
(37)



(35, R=Et, R'=H)

(38, R=H, R'=Me)

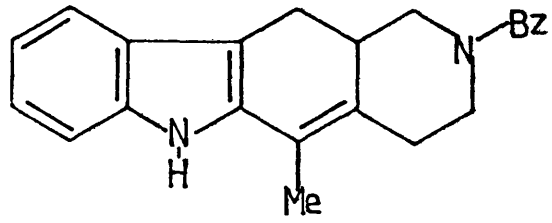
Route 7



(39)

1. HCOOH
2. Na/NH_3
3. Pd/C

Ellipticine



1. H^+
2. Na/NH_3
3. Pd/C

11-Demethylellipticine

N-p-toluenesulphonyl derivative (30) using 6N hydrochloric acid in dioxan at room temperature. The use of these milder conditions allowed the preparation of a series of derivatives including 8,9-dimethoxy and 8,9-methylenedioxyellipticine (31 and 32).

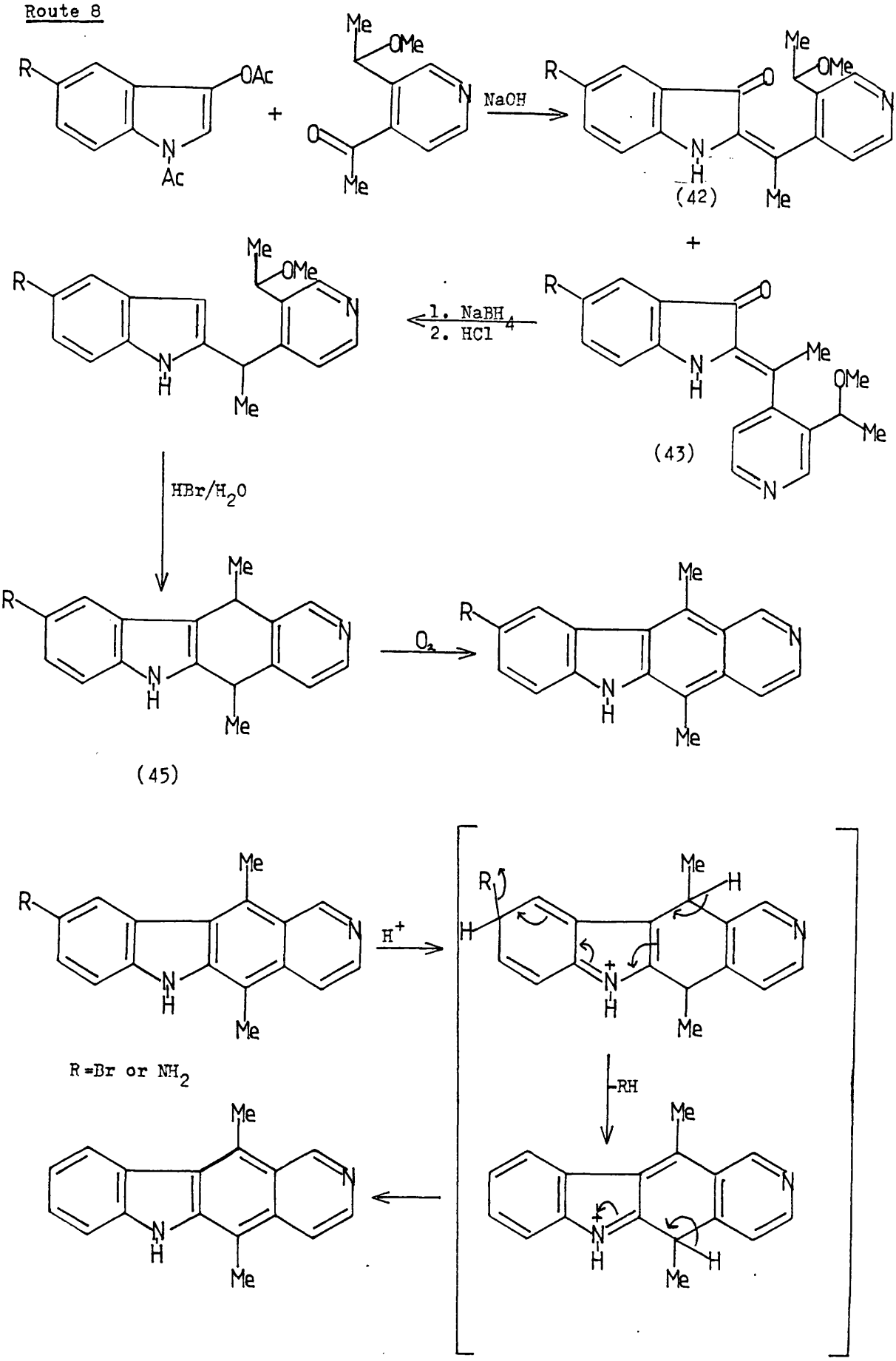
A Swiss group have patented a modification[23] of the basic route in which they effect the cyclisation of a 2-substituted carbazole (33) with phosphorus oxychloride to give ellipticine after dehydrogenation (Route 5).

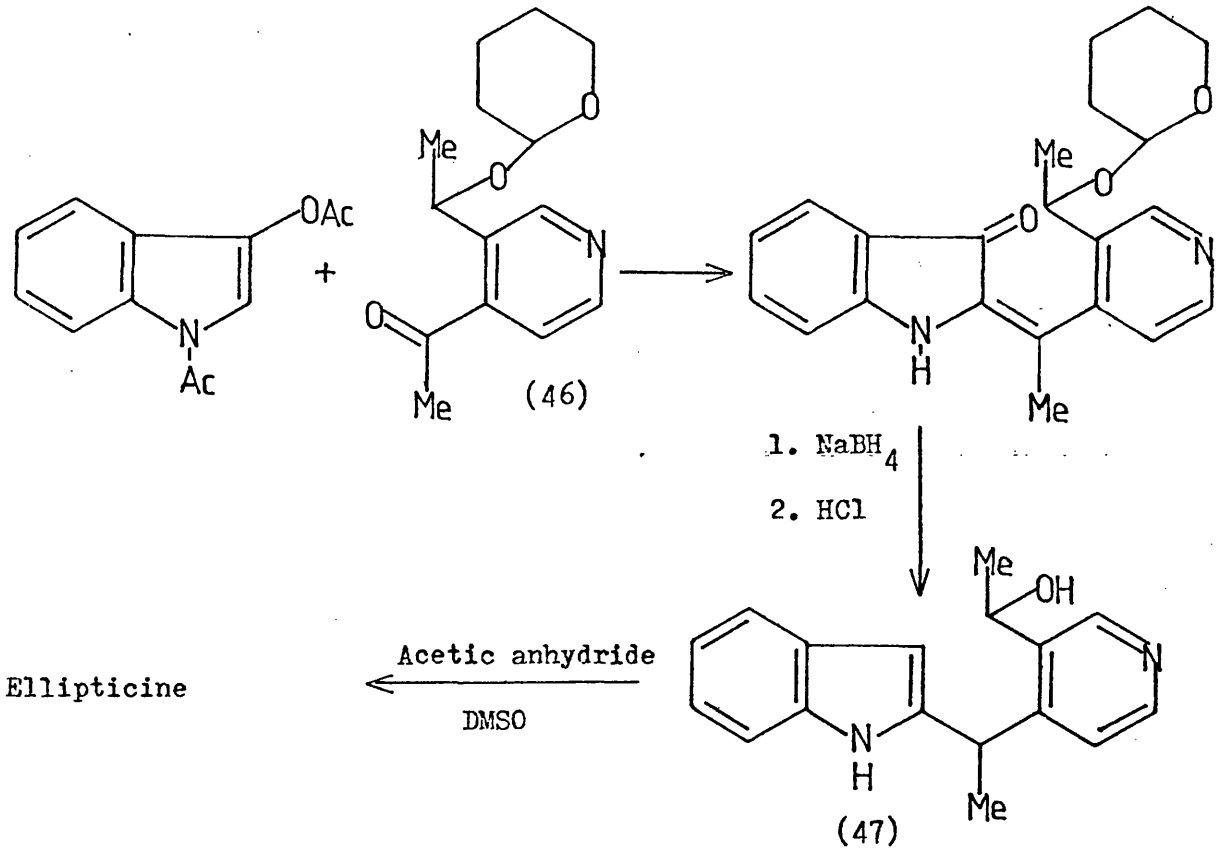
French chemists have also devoted a great deal of effort in this field and a group led by Le Goffic[24] devised two methods the first giving 11-demethylellipticine from the piperidone (35) after cyclisation with acetic anhydride followed by debenzylation and dehydrogenation (Route 6).

The preparation of the gramine derivative (34, R=Me, R=H) required for the synthesis of ellipticine itself proved more difficult and a second synthetic pathway was developed employing the alternative gramine derivative (36) (Route 7). Reaction with the enamine (37) gave the piperidone (38) which when reacted with sodium acetylide gave the alcohol (39). Cyclisation was effected in formic acid and ellipticine was obtained as before in a respectable 24% yield from indole.

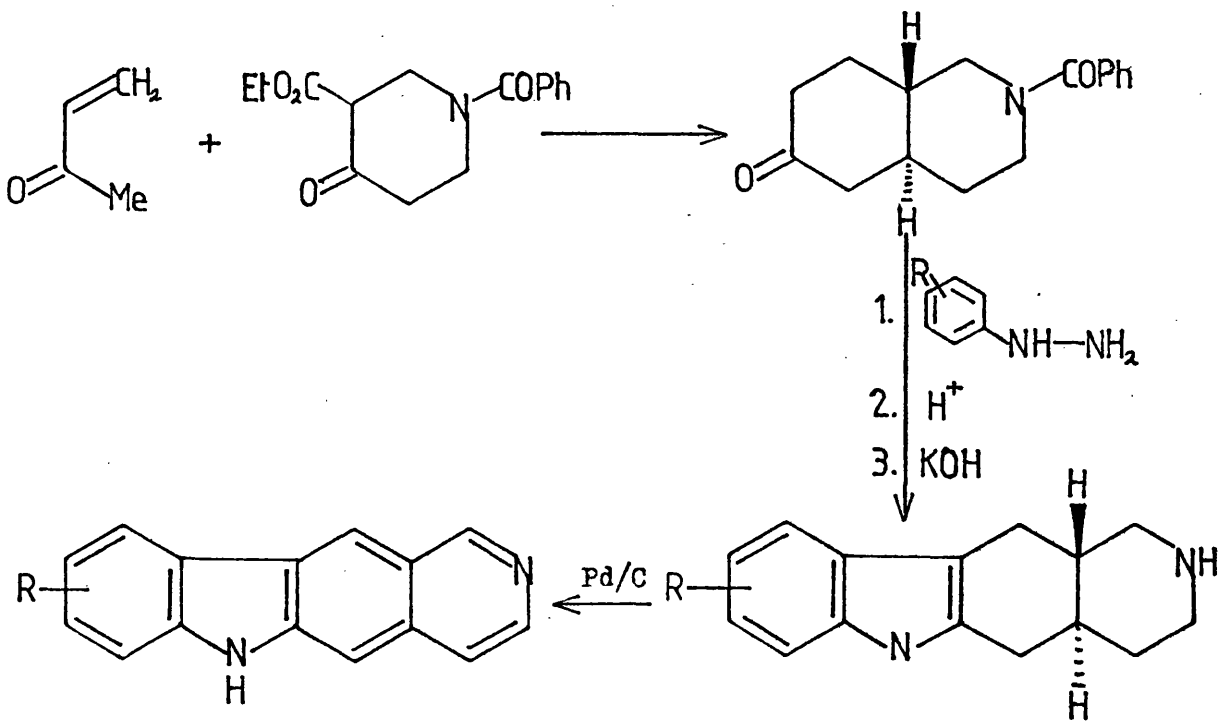
Another new approach to the tetracyclic system was developed the same year in England by Kilminster and Sainsbury[25] (Route 8). Condensation of the diacetylindole(40,R=H) with 4-acetyl-3-(1-methoxyethyl) pyridine (41) furnished the E-and Z-2-ethylidene indolin-3-ones (42 and 43) and the corresponding indole (44) was obtained after subsequent treatment with sodium borohydride and hydrogen chloride.

Route 8


R
OAc
N
Ac
+
Me
OMe
O
N
Me
NaOH
H
(42)
1. NaBH4
2. HCl
HBr/H2O
(43)
O2
(45)
H+
R=Br or NH2
RH

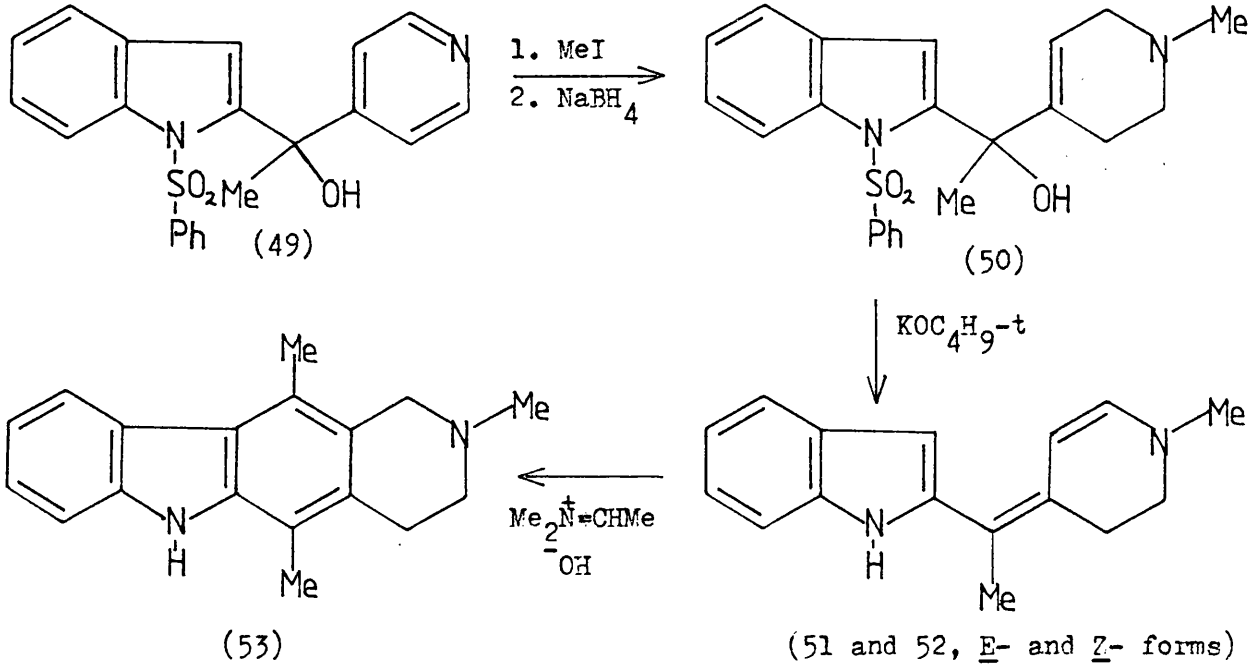


Route 9



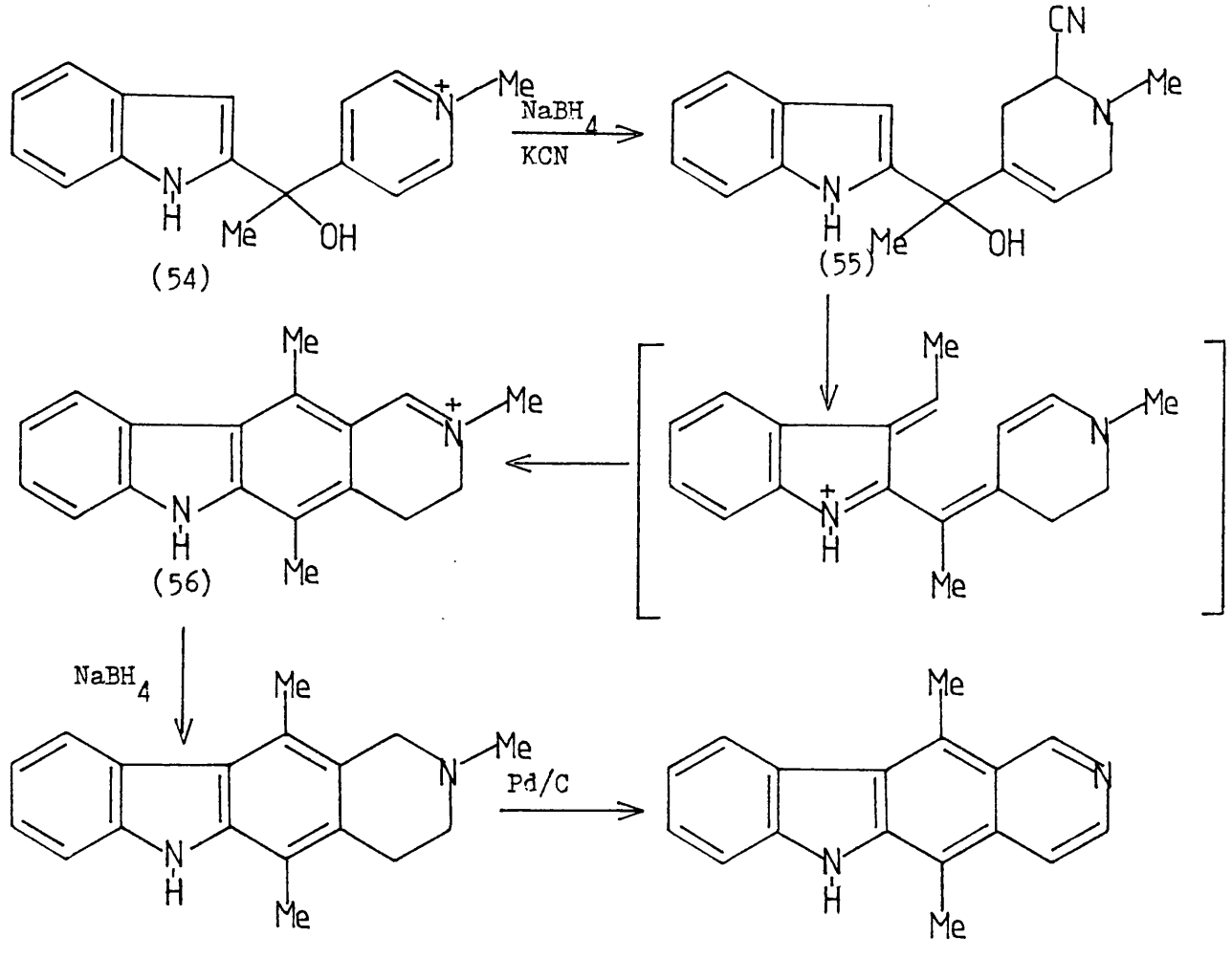
R=7-F, 9-F, 7-MeO, 9-Me

Route 10



(49) (50) (51 and 52, E- and Z- forms) (53)

Route 11



(54) (55) (56) (53)

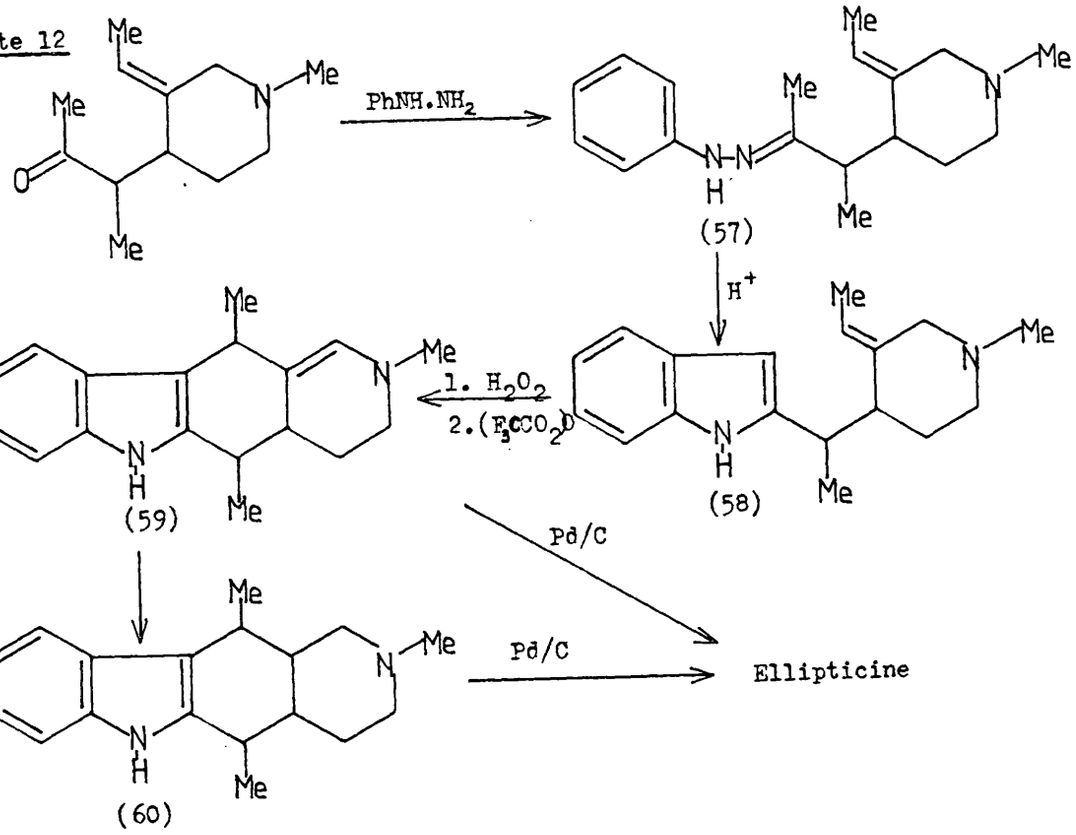
Ring closure was achieved using 40% aqueous hydrogen bromide and the intermediate (45) oxidised to ellipticine spontaneously during elution through a silica column. The overall yield from indole was 27% and this procedure was used to prepare several derivatives[26] including 9-phenylellipticine. When this method was used to prepare other 9-substituted derivatives it was found that the desired product was always contaminated with considerable amounts of ellipticine. Thus in modified sequences disappointing yields of 9-bromo and 9-aminoellipticine were obtained[27]. Since the substituents in these cases were 'good leaving groups' they were able to participate in the aromatisation of the dihydro compounds (45,R=Br or NH_2) probably through the mechanism outlined.

Attempts to overcome this problem[27] included the use of the pyridine (46) from which the alcohol (47) was obtained. Oxidation of this compound with acetic anhydride in dimethyl sulphoxide gave the acetyl derivative which immediately cyclised to ellipticine. Further developments of this procedure led to an entirely new route[28] which will be described in detail later. (Page15).

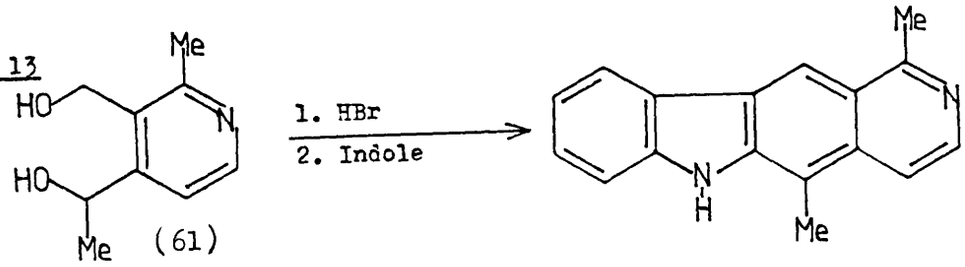
The following years saw the publication of more synthetic routes to the ellipticines by chemists from all over the world. Indian workers[29] prepared several pyrido (4,3-b) carbazoles using a similar scheme to that devised by Stillwell. They claimed better yields than the Americans but did not actually quote any so the potential of this revised method is unclear (Route 9).

A French team led by Potier[30] have developed three routes to ellipticine which they consider mimic, to a certain extent, the biosynthesis of the alkaloid. In the first route (Route 10) the alcohol (49) was obtained from a reaction of 2-lithio-1-benzene sulphonylindole with 4-acetyl pyridine. Quaternisation was effected

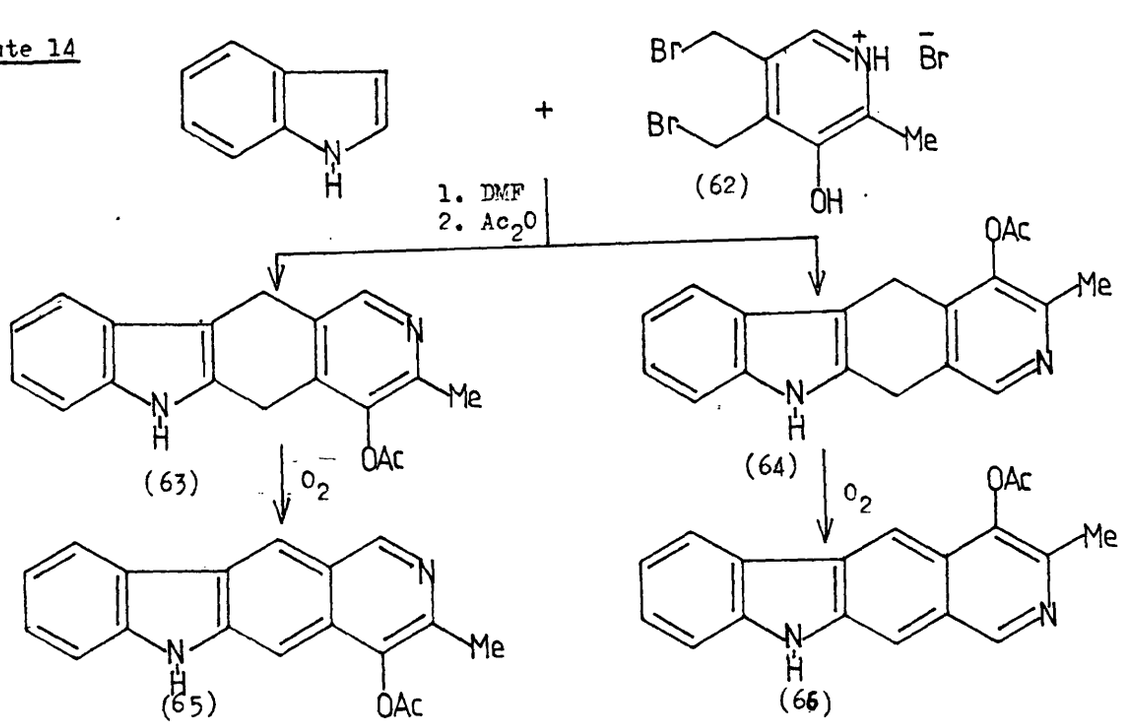
Route 12



Route 13



Route 14



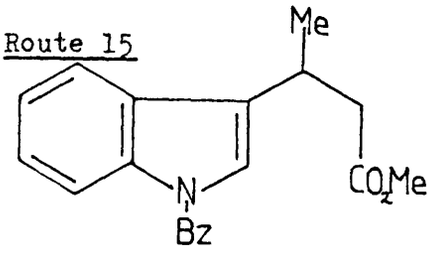
with iodomethane and treatment with sodium borohydride gave the tetrahydropyridine (50). This compound was reacted with potassium t-butoxide to give the isomeric (E-and Z-)dienamines (51 and 52) which in turn gave 2-methyl-1,2,3,4-tetra hydroellipticine (53) when treated with the Mannich reagent from the reaction of acetaldehyde and methylamine.

The same tetrahydro derivative was obtained from a slightly different sequence of reactions (Route 11) when the alcohol (49) was hydrolysed to the indole and the corresponding quaternary salt (54) reduced with sodium borohydride in an excess of potassium cyanide to give (55). This product when treated as before with the Mannich reagent gave the ring closed compound (56) which was reduced with sodium borohydride to afford the N-methyl-tetrahydro derivative (53) as before. Final conversion to ellipticine was achieved by heating with palladium on charcoal and in both routes the overall yield from the alcohols is of the order of 15%.

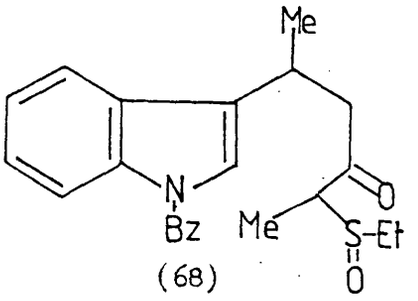
This groups' third effort[31] (Route 12) includes a Fischer-indole cyclisation of the phenylhydrazone (57) to give the indole(58) which on treatment with hydrogen peroxide and trifluoroacetic anhydride gave the hexahydro-tetracycle (59). Aromatisation of this product was accomplished directly by heating with palladium on charcoal; alternatively the octahydro derivative (60), prepared by the reduction of (59) was oxidised to ellipticine. In either case the yield from the hydrazone was 18-20% and although these routes offer certain advantages the final dehydrogenation step is not desirable when labile substituents are present.

Kametani and his workers have also recently reported some ingenius routes [32,33] to the tetracyclic system (Routes 13 and 14). The dihydroxy compound (61) when dibrominated and reacted with indole

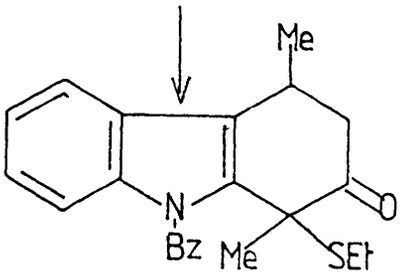
Route 15



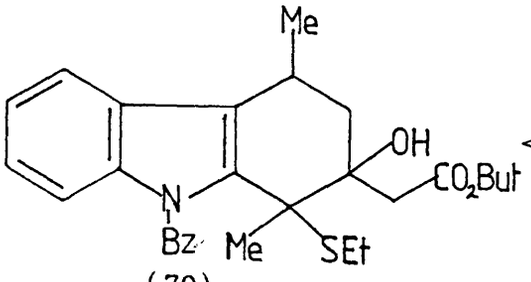
(67)



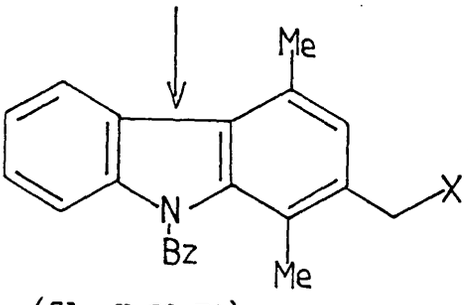
(68)



(69)

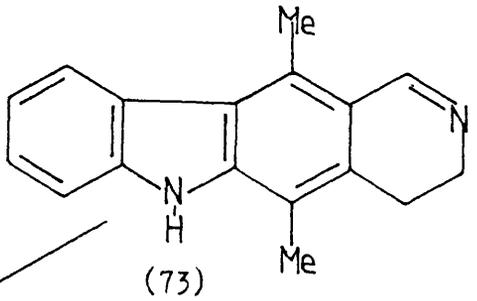


(70)



(71, X=CO_2Et)

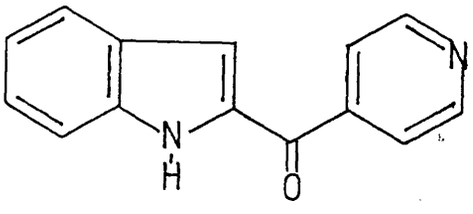
(72, X=CH_2NHCHO)



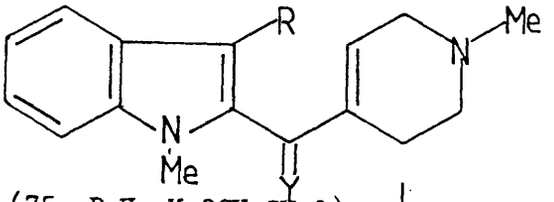
(73)

Ellipticine

Route 16

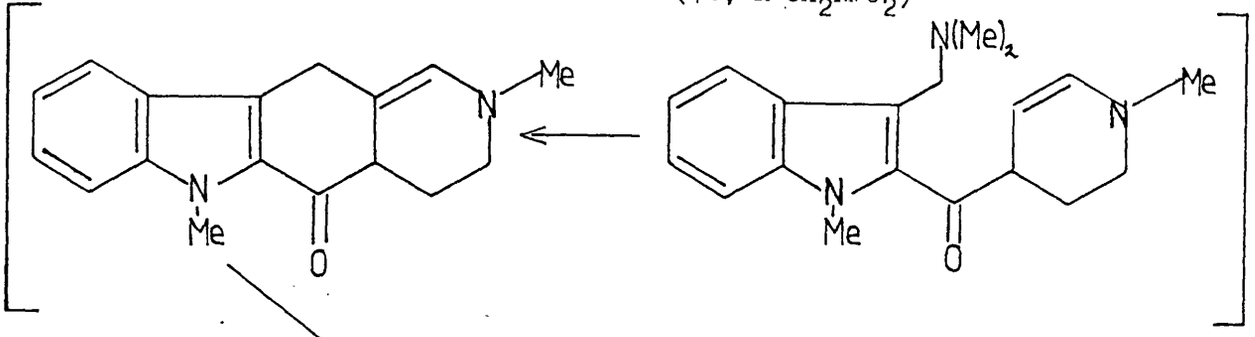


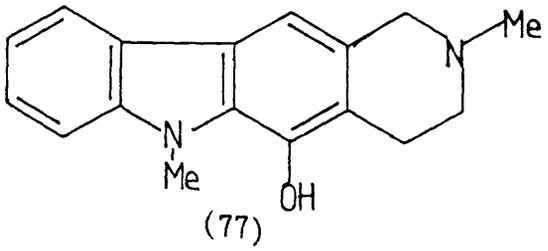
(74)



(75, R=H, Y=OCH_2CH_2O)

(76, R=CH_2NMe_2)





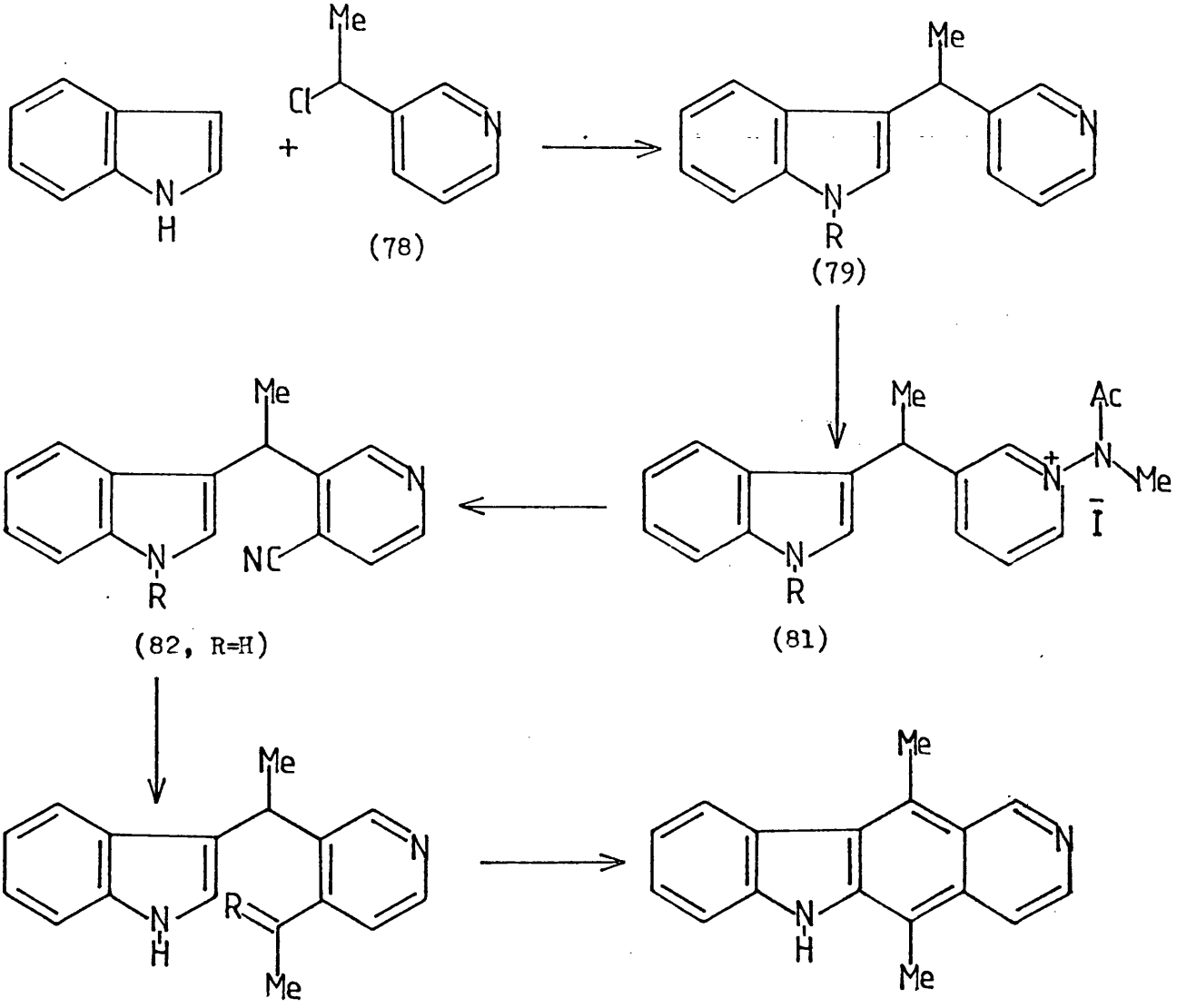
(77)

gave olivacine in 30% yield. Similarly when 4,5-dibromomethyl-3-hydroxy-2-methyl pyridinium bromide (62) and indole in dimethyl formanide were reacted and subsequently acetylated the two isomeric products (63 and 64) were obtained. These last two compounds slowly oxidised to the fully aromatic species (65 and 66) on standing.

Another Japanese publication[34] describes the synthesis of ellipticine in 23% yield from methyl-1-benzylindole-3-butyrate (67) (Route 15). This compound on treatment with the lithium salt of diethyl sulphoxide gave (68) which in turn yielded the ring closed product (69) when heated with trifluoroacetic acid. The carbonyl group in this compound was attacked with t-butyl lithioacetate to give (70) as a mixture of stereoisomers from which the carbazole (71) was obtained after heating with toluene-p-sulphonic acid in a boiling xylene/ethanol mixture. A series of steps converted this material into N-(1,4-dimethyl-9H-carbazol-2-yl) ethyl formamide (72) (c.f. Govindachari's method, page 10), which was cyclised using a modified Bischer-Napieralski reaction to give the 3,4-dihydro derivative (73) which was dehydrogenated by heating with palladium on charcoal. This route offers a moderate yield but has the disadvantage of including a large number of steps.

A synthetic effort directed towards the preparation of a 5-hydroxylated ellipticine derivative has recently been published by Martinez and Joule[35]. The isonicotinoylindole (74) was converted to the protected compound (75) and subjected to a Mannich reaction to give the disubstituted indole (76). The protecting function was removed and subsequent heating in degassed 50% acetic acid under nitrogen yielded 5-hydroxy-5, 11-didemethyl-2, 6-dimethyl-1, 2, 3, 4-tetrahydroellipticine (77) (Route 16).

Route 17



(78)

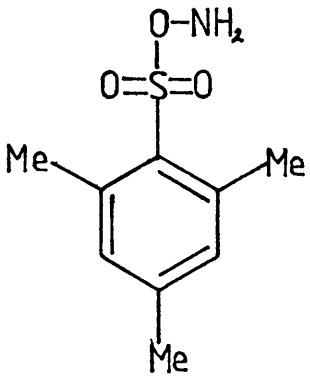
(79)

(81)

(82, R=H)

(83, R=NH)

(84, R=O)

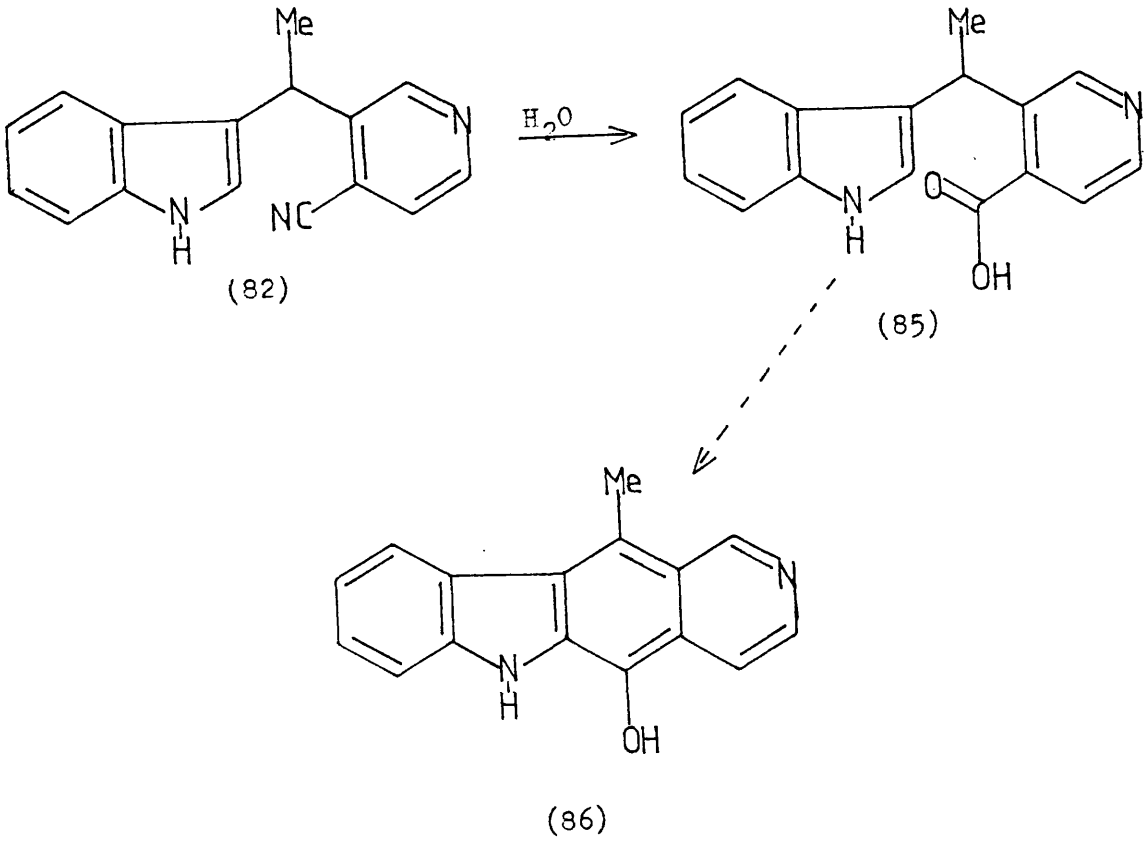


(80)

As can be appreciated from the numerous synthetic routes to the ellipticine system reported here many excellent chemists have spent a great deal of time attempting to devise an efficient preparative procedure. One more synthesis developed in this laboratory[28], has yet to be described and while it is not without its disadvantages we feel that it is perhaps the most versatile route announced to date. (Route 17).

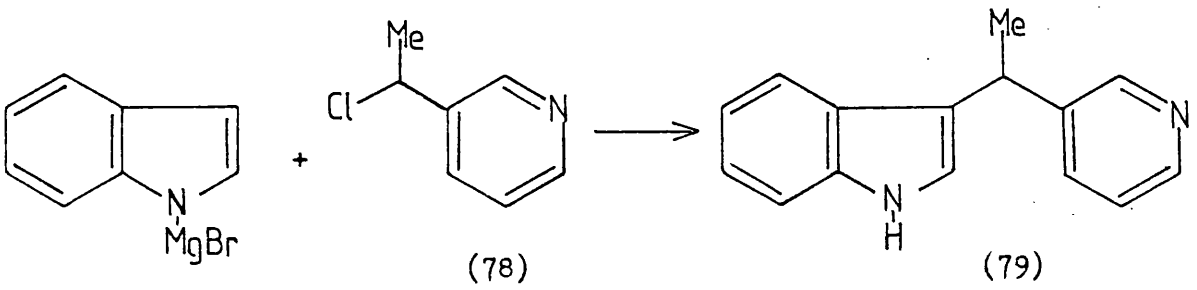
The development of the original Kilminster and Sainsbury route led to the use of the protected pyridine alcohol(46). During the course of the study an efficient route to 4-acetylpyridines was developed and this procedure was used to greatest effect when it was found that the reaction of 3-(1-chloroethyl) pyridine (78) with indolylmagnesium bromide afforded a "1,1-product" (79) (cf. Woodwards 2,1-product and acetylation procedure).

It was visualised that the key acetyl intermediate (84) should be attainable from the corresponding nitrile (82) by reaction with methylmagnesium bromide followed by hydrolysis of the resulting imine. To prepare the desired cyanide (82) it was necessary to activate the β-position of the pyridine ring towards nucleophilic attack and at the same time block the two α-positions. This was achieved by amination of the pyridine nitrogen atom using O-mesitylsulphonylhydroxylamine [36,37] (80) followed by acetylation and methylation to give the salt (81). Reaction with cyanide under aqueous conditions gave the nitrile (82) which, however, proved inert to attack by Grignard reagent. This problem was overcomeby employing methyl lithium to give the imine (83) which was hydrolysed with 20% acetic acid when spontaneous cyclisation and aromatisation occurred. The yield of ellipticine from the pyridoindole (79) was 65% and the scope of the synthesis was examined with encouraging results when 11-demethyl, and 8,9-methylenedioxy-ellipticine were prepared using modified reactions.

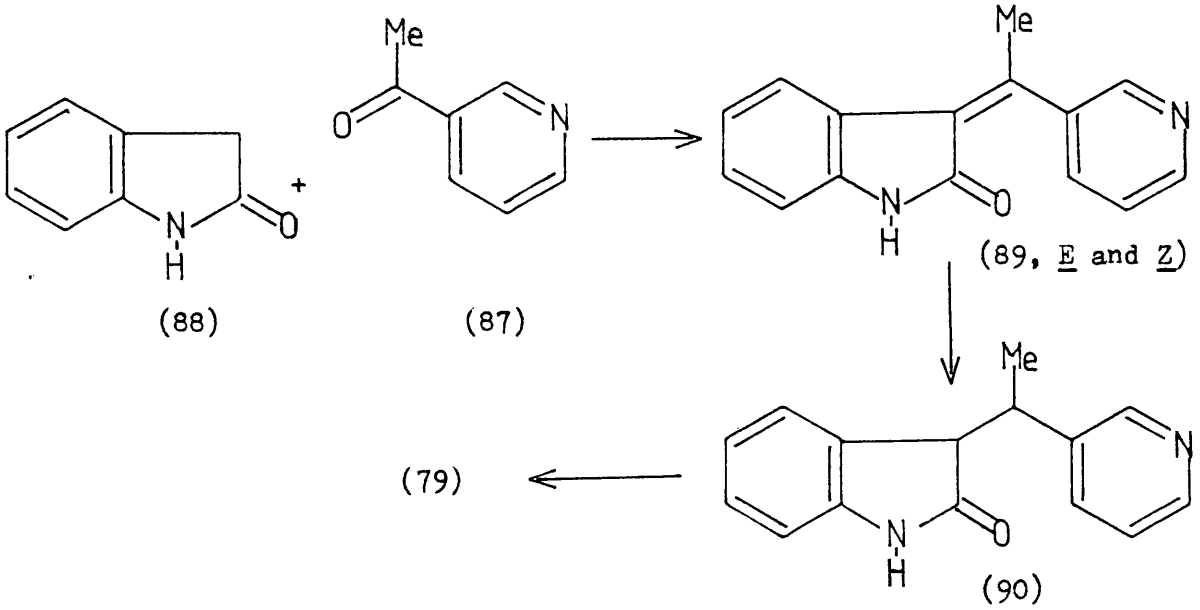

Me
N
H
NC
(82)
H_2O
Me
N
O
N
H
OH
(85)
Me
N
N
H
OH
(86)

It was at this time that the work described in this thesis was beginning and our main aim was to explore further the scope of the new synthesis. We especially wanted to synthesise hydroxylated ellipticine derivatives since the anti-tumour activity of 9-hydroxyellipticine appears to be so good. We envisaged the nitrile (82) lending itself to the preparation of 5-hydroxyellipticine (86) since hydrolysis to the corresponding carboxylic acid (85) would leave us with only cyclisation and aromatisation conditions to investigate. By synthesising this derivative we hoped to gain an insight into the structure-activity relationship associated with the hydroxyl function. We also considered that it would be informative to prepare derivatives with extended alkyl chains in either position 5 or 11 since this might well modify the cell permiability characteristics of the molecule.

It was with these basic aims then that the work described hereinafter began.

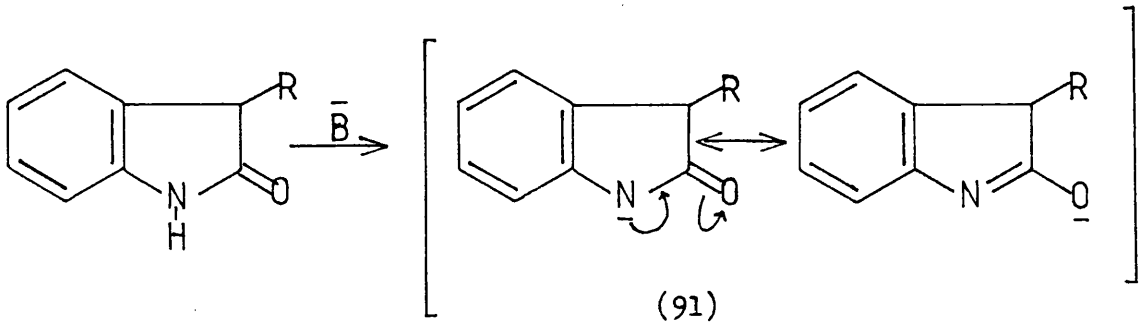


(78) (79)



(88) (87) (89, E and Z)

(79) (90)



(91)

DISCUSSION

The Synthesis of Ellipticine Derivatives from 3-(1-(3-Pyridyl)ethyl) indole (79)

Having decided to employ the route developed by Sainsbury and Schinazi[28] in our attempts to synthesise ellipticine derivatives we were faced with the problem of preparing the pyridoindole (79) in substantial quantities. The reaction of indolylmagnesium bromide with 3-(1-chloroethyl) pyridine (78) gives the compound directly but yields using this method are variable and often low so we first decided to investigate an alternative preparation.

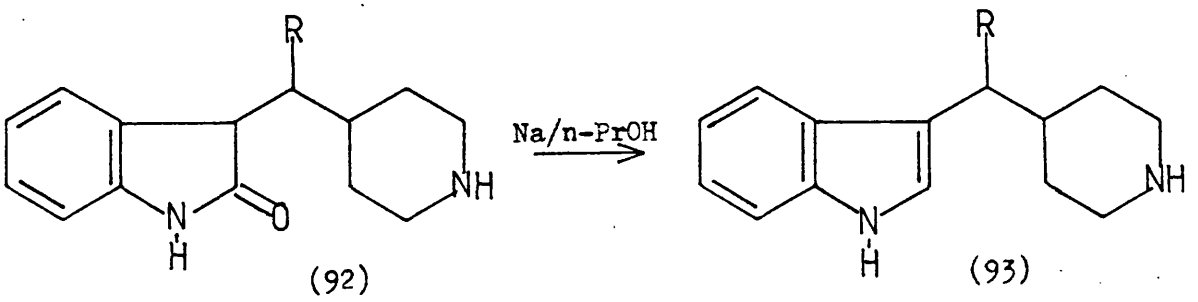
The Reduction of Oxindoles

The oxindolylidene derivatives (89) can be prepared in good yield from the reaction of 3-acetylpyridine (87) with oxindole (88) in pyrrolidine solution[38]. Reduction of this product with sodium borohydride gives the oxindole (90) also in good yield. We decided to employ this route to prepare this oxindole (90) and then find conditions suitable for subsequent reduction to the desired indole (79).

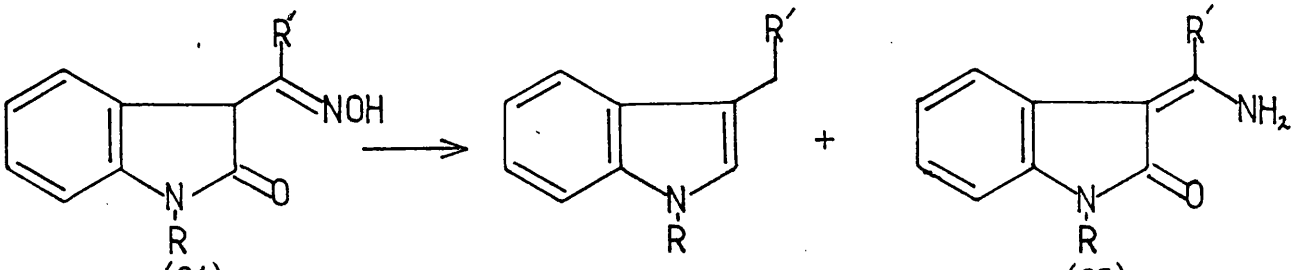
Over one hundred years ago Baeyer reported[39] the conversion of oxindole to indole by passing the vapour over hot zinc; however this method appears impractical, especially for complex derivatives.

Lithium aluminium hydride (LAH) effectively reduces N-alkylated oxindoles to indoles[40] but it is generally accepted that N-unsubstituted derivatives are not satisfactorily reduced by this reagent, probably because the anion (91), which resists attack by nucleophilic species, is formed in the presence of a strong base, such as LAH.

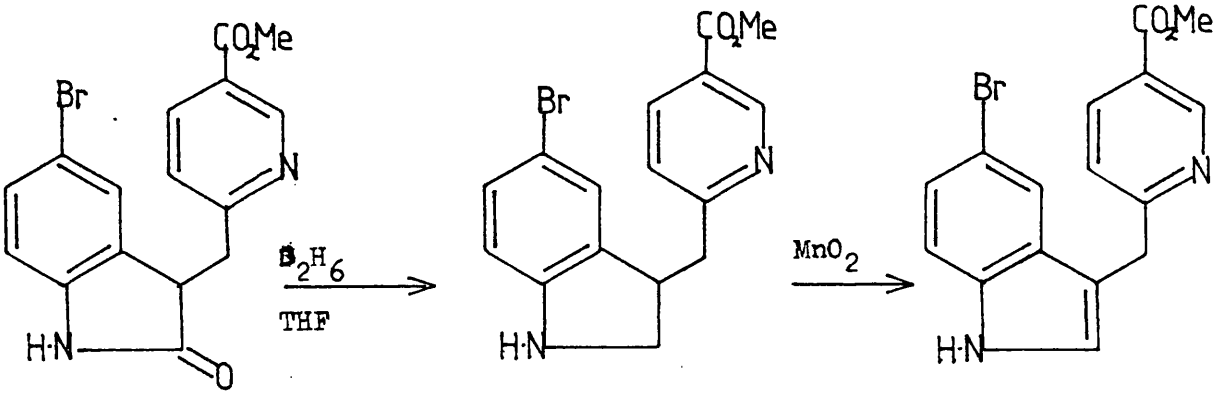
Sodium in alcohol is a reagent combination that is said to reduce oxindoles, but once again evidence suggests that only highly alkylated derivatives are converted to indoles.[41] Italian



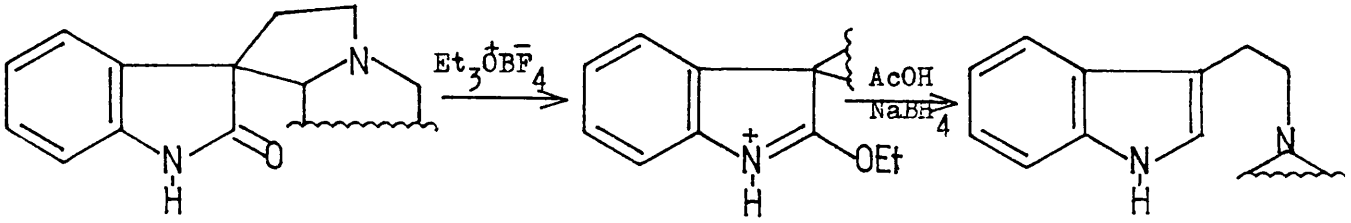
(92) (93)



(94) (96) (95)

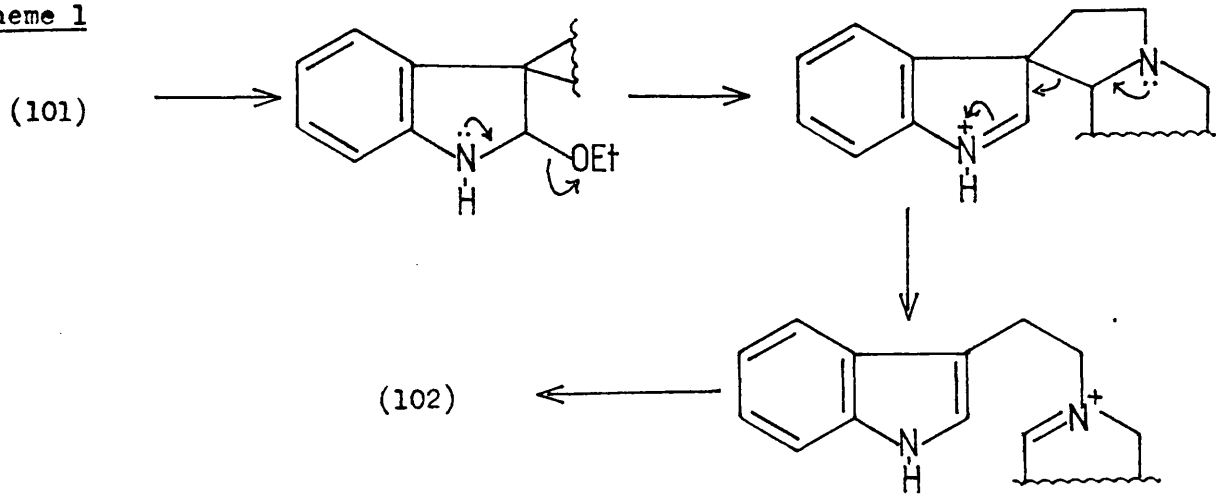


(97) (98) (99)



(100) (101) (102)

Scheme 1



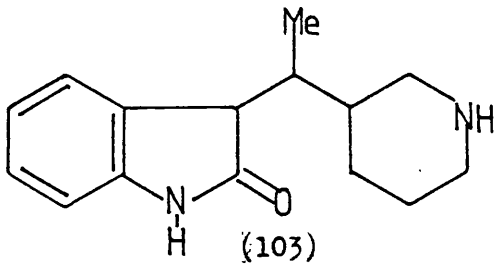
workers have reported[42] however, that the oxindolyl derivative (92) is reduced by heating with sodium in boiling n-propanol to give (93).

Wenkert et al[43] discovered that when 3-acyloxindole oximes (94) are catalytically hydrogenated they obtain mixtures of 3-(α-aminoalkylidine) oxindoles (95) and 3-alkylindoles (96). Interestingly, indole N-unsubstituted compounds give indolic products whereas N-alkylated derivatives afford only the α-aminoalkylidines.

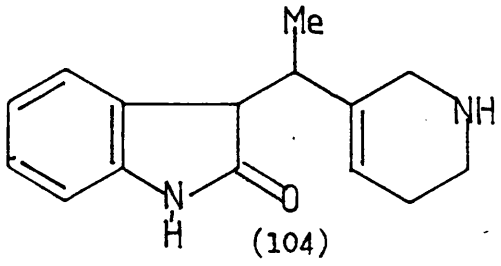
Julia and co-workers[44] used diborane to effect an oxindole to indole conversion whilst working on lysergic acid analogues. Thus (97) was reduced to the indoline (98) which was treated with manganese dioxide to furnish theindole derivative (99). Other successful examples of the use of this reagent to reduce oxindoles have been reported[45].

Meerwein's reagent, triethyloxonium tetrafluoroborate, reacts with amides to form imine ethers and these salts may be converted to the corresponding amines. Aimi et al[46], for example, have prepared the indole (102) from the oxindole alkaloid (100). Treatment of (101) with sodium borohydride in ethanol gave only starting material but when this reaction was repeated in glacial acetic acid the desired product (102) was formed, presumably by the mechanism shown. (Scheme 1).

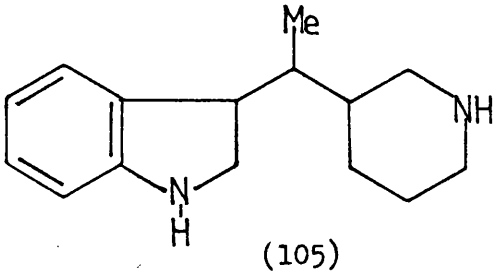
Despite the successes recorded above previous work[47] in this laboratory has shown that most of these methods are ineffective when the oxindole (90) is used. For example, Kilminster found that treatment of (90) with LAH in boiling tetrahydrofuran gave only intractable tars, while experiments with sodium and propanol gave multi-component products, the mass spectra of which suggest the formation of the hexahydro (103) and tetrahydro (104) derivatives of the oxindole. There is evidence to suggest that a small amount of the desired product (105) is formed but none could be isolated from the reaction mixture in a pure state. Similar



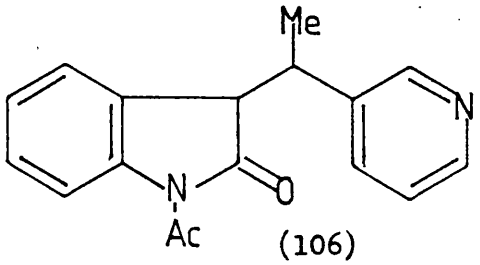
(103)



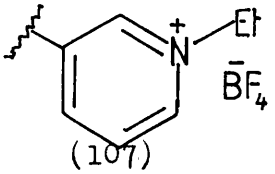
(104)



(105)

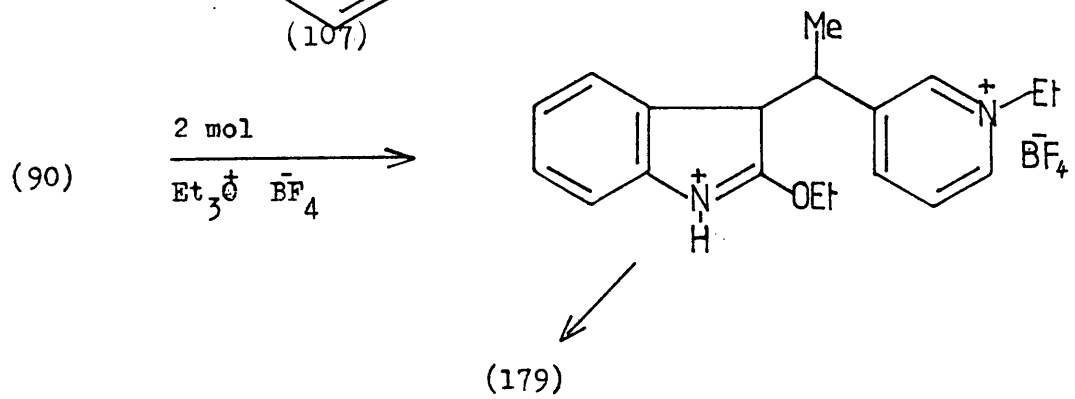


(106)



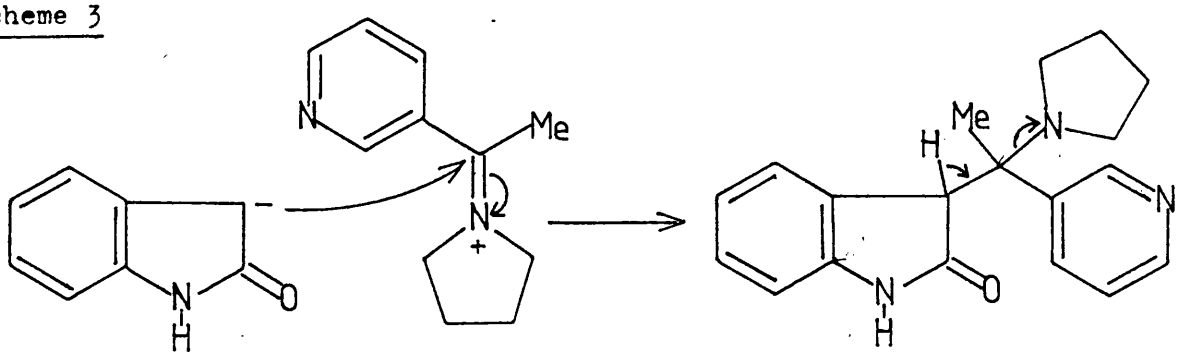
(107)

Scheme 2

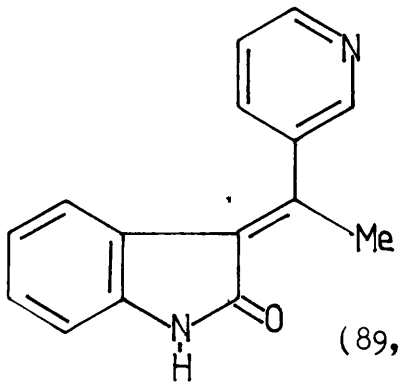


(179)

Scheme 3

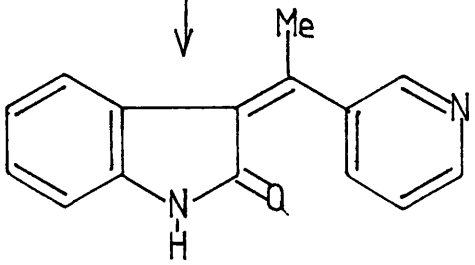


(108)



(89, E-form)

+



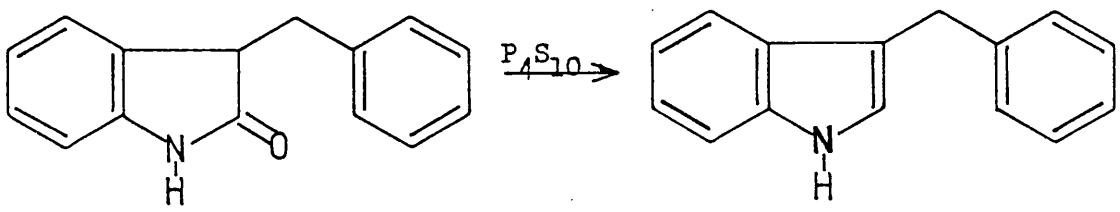
(89, Z-form)

reactions employing the N-acetyl derivative (106) or the oxindolylidine (89) were also disappointing. Reactions of (90) with diborane under a variety of conditions were found to give mainly starting material while treatment with Meerwein's reagent gave only the pyridinium salt (107) and thus the envisaged sequence (Scheme 2) could not be pursued.

Despite these failures the appeal of this general route to ellipticine precursors was such that we decided to initiate further attempts to effect the oxindole to indole conversion.

Preparation of the Oxindole (90)

A considerable amount of work has been published[48] on the reaction of oxindoles with carbonyl compounds and results show that reactions with aldehydes proceed much more smoothly than those with ketones. It has been found, however, that if pyrrolidene is used to form the enamine system (108) reaction with ketones can proceed expeditiously, affording the appropriate oxindolylidenes in high yields (Scheme 3). Thus heating oxindole, 3-acetylpyridine and pyrrolidine in boiling benzene gave (89) in 80% yield as red prisms. The infra-red spectrum of this compound shows a peak at 1700cm^{-1} due to the carbonyl absorption while peaks at 3200 and 1620 cm^{-1} correspond to the indole N-H bond and the exocyclic double bond stretchings respectively. The pmr spectrum displays the indole nitrogen proton resonating as a broad singlet at δ10.0 ppm while a three proton singlet at 2.8 ppm corresponds to the methyl group. The aromatic protons absorb as a complex signal between 8.8-6.0 ppm. From this data it is evident that only one of the two possible geometric isomers is present since the methyl proton resonances are unlikely to appear at the same chemical shift position in both the E and Z-forms. Common sense would suggest that the better



(109) (110)

spatial arrangement provided by the E-isomer would be preferred. The low field position of the methyl singlet appears to support this view but one cannot be absolutely sure for in the E-form these protons lie in the deshielding zone of the adjacent carbonyl group.

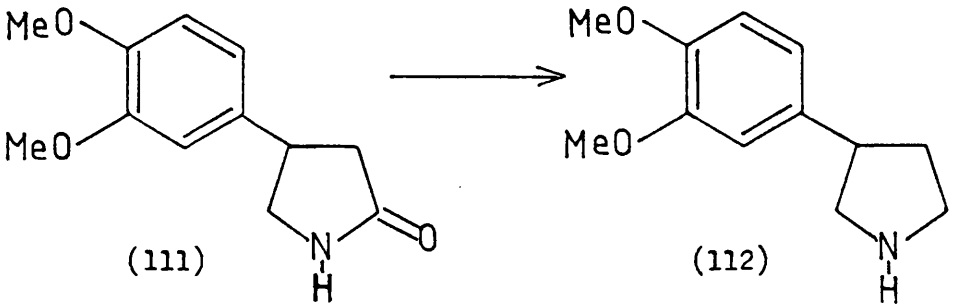
Reduction of this product with sodium borchydride yielded a yellow gum which crystallized only after standing for a period of several months. The mass spectrum of the gum shows a molecular ion peak at m/e 238 corresponding to the reduced oxindolylidene (90), while the pmr spectrum is in accordance with that expected of such a structure.

Attempts to reduce the Oxindole (90)

Plieninger and Werst[49] used phosphorus pentasulphide (P_4S_{10}) to reduce 3-benzyloxindole (109) to 3-benzylindole (110). These authors heated the reagent and substrate together in pyridine at 110°C for several hours and on work-up they obtained a red oil which when treated with Raney nickel in ethanol furnished 3-benzylindole in 80% yield. We decided to follow this procedure to see if we could emulate the success of the German workers.

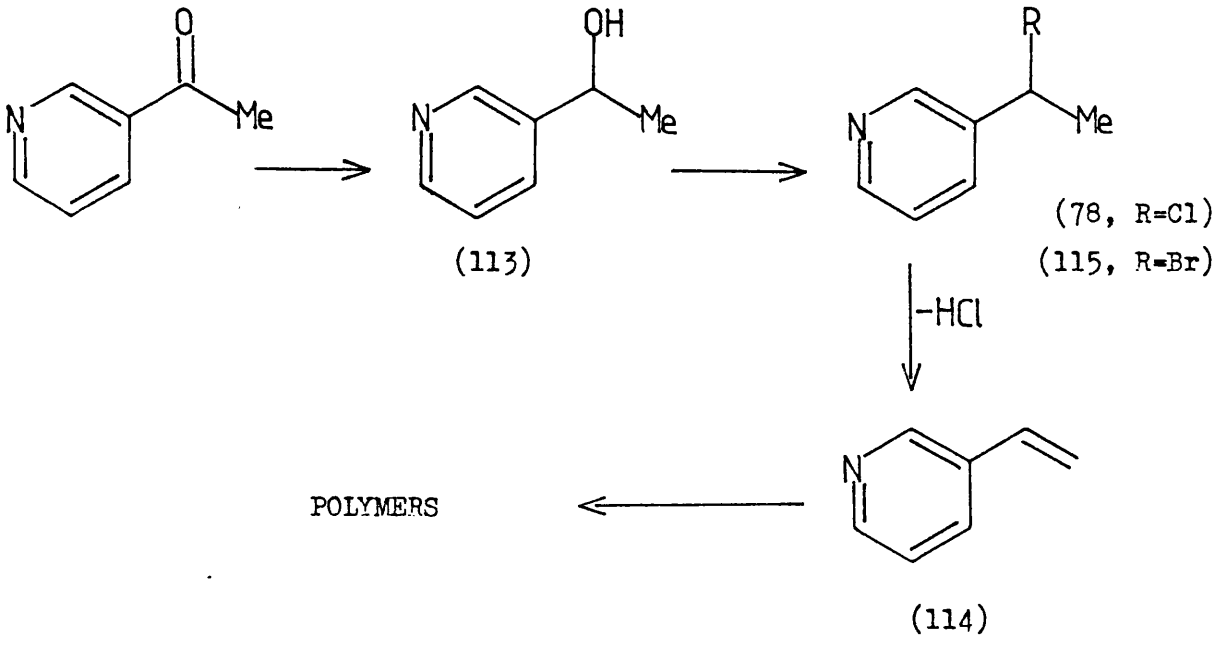
Phosphorus pentasulphide was prepared[50] by heating yellow phosphorus with carbon disulphide to 170-200° in naphthalene solution which, on cooling, afforded a yellow solid which crystallized from carbon disulphide as needles (m.p. 280-285°, lit[51] 286-290°). Using this material we repeated the German's procedure but we were disappointed to obtain an orange gum which displayed a prominent peak at 1700 cm^{-1} in the infra-red spectrum. Clearly reduction had failed.

A recent paper by Japanese workers[52] describes the use of sodium acyloxyborohydrides as a new reagent for the reduction of carboxamides to amines. They record that primary and secondary amides are reduced easily by equimolar mixtures of sodium borohydride and



(111) (112)

Scheme 4



(113) (78, R=Cl) (115, R=Br) (114)

acetic acid but that tertiary amides require the use of trifluoroacetic acid. Thus they claim a 64% yeild of N-ethylindoline from N-acetylindoline and a 60% yield of the amine(112), from the amide(111). In an attempt to apply this method to our system the oxindole (90) was heated for periods of up to twelve hours with a ten molar excess of sodium borohydride and acetic acid in dioxan. Work-up invariably yielded only starting material and similar reactions in trifluoroacetic acid also proved unproductive.

We decided that before abandoning this approach we would employ diborane in an attempt to effect the reduction by heating for extended periods. Thus the oxindole (90) was treated with diborane (from sodium borohydride and borontrifluoride etherate) and heated for up to five days. Success eluded once again however and we finally decided to switch our attention to alternative methods for the preparation of the indole (79).

Since N-alkylated oxindoles can be reduced to the corresponding indoles using LAH this route may have applications for the preparation of 6-alkylated ellipticines. However initial pharmacological evaluation suggests that this type of derivative may not be as active as 6H-pyrido (4,3-b) carbazoles and so we decided not to pursue this research further.

Reaction of Indolylmagnesium bromide with 3-(1-Chloroethyl) pyridine

At this stage we decided to revert to the reaction of the Grignard reagent with the pyridine (78) in the hope of optimising the yield.

The halopyridine was prepared from 3-acetylpyridine by firstly a sodium borohydride reduction and then treatment of the resultant alcohol (113) with thionylchloride. The product was obtained as a yellow oil which proved unstable if not kept cool, decomposing to the vinyl derivative (114) and then polymerising (Scheme 4). Work in this laboratory[53] has shown that the bromo analogue (115) is

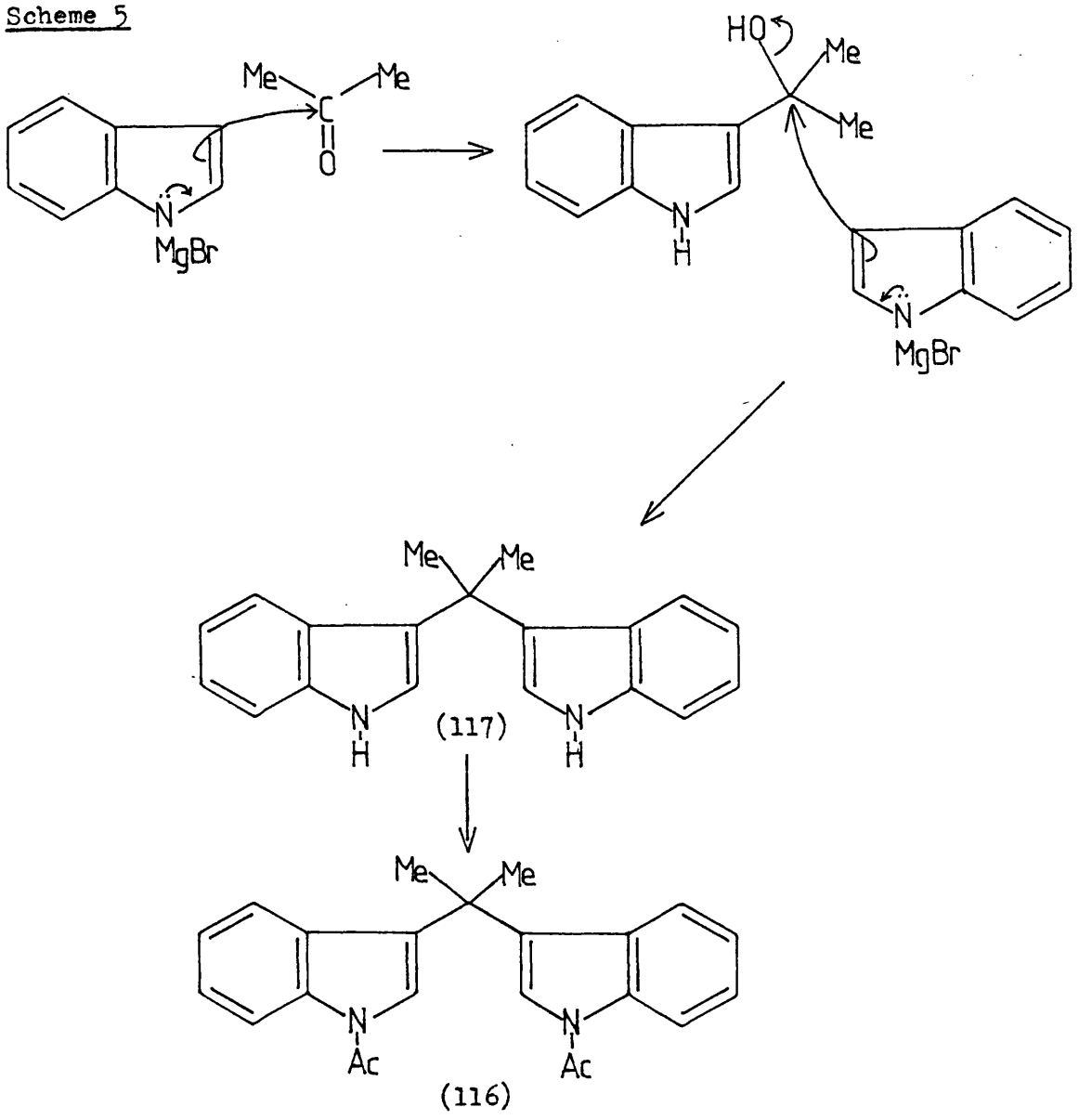
even more labile and that reactions between this derivative and indolylmagnesium bromide are not productive.

As anticipated initial reactions of the indole Grignard reagent and (78) proved disappointing. Low yields of the desired product were obtained while large quantities of unreacted pyridine and indole remained. At first we used a 2:1 molar excess of the Grignard reagent but we later altered this to a 50% excess since the yields remained the same, between 10 and 20%. Extended reaction periods proved not to be beneficial and when elevated temperatures were employed the yield fell, no doubt due to the thermal instability of the pyridine. Many reactions were performed under varying conditions and results suggested that larger scale reactions were less productive.

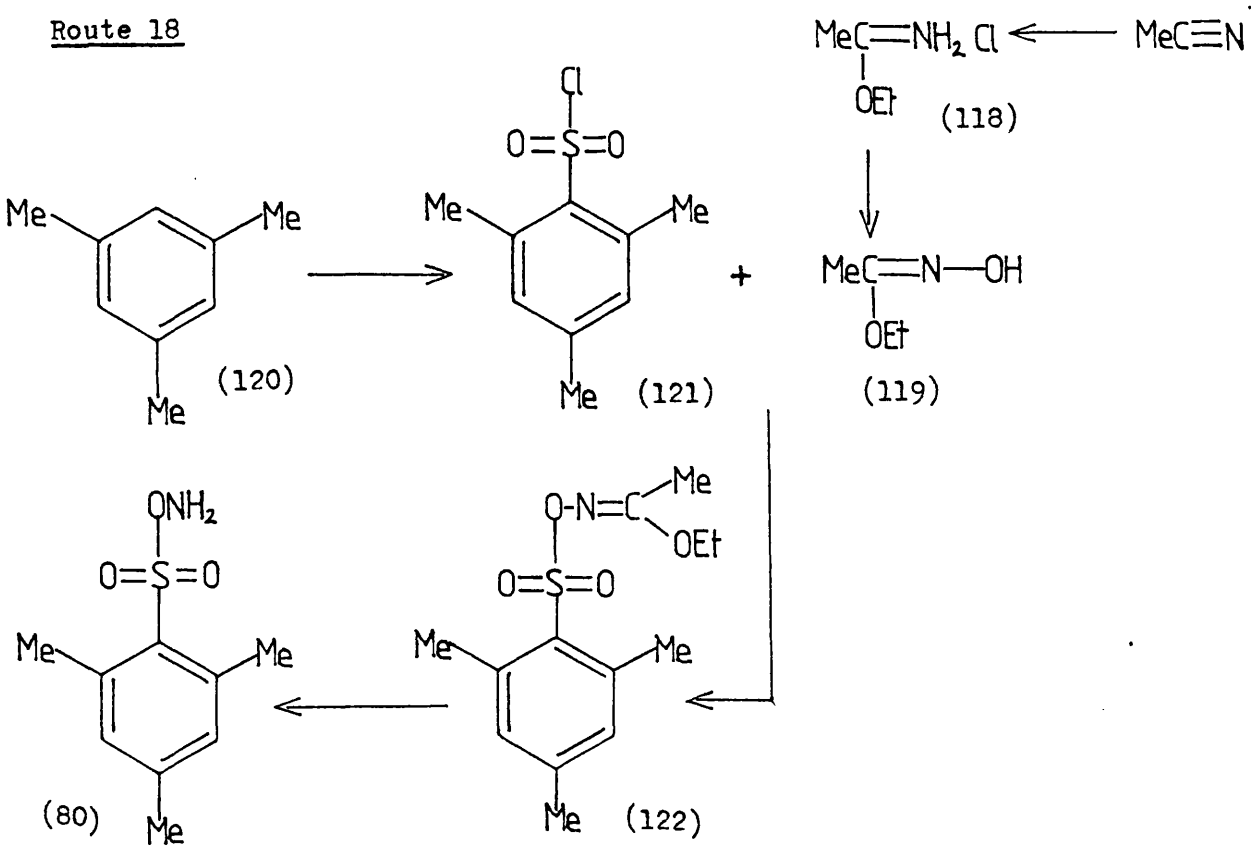
Eventually enough of the indole (79) was accumulated to enable us to proceed to the next step which involved indole N-acetylation by heating in a boiling solution of acetic anhydride with a trace of triethylamine. This product crystallized from ethanol as colourless prisms and in the infra-red spectrum displays a large absorption at 1700 cm^{-1} corresponding to the N-acetyl carbonyl group. The pmr spectrum shows the hydrogen atoms of the bridging ethane unit to resonate as a three proton doublet (J=7Hz) at 1.55 ppm and a one proton quartet (J=7Hz) at 4.22 ppm. A three proton singlet at 2.45 ppm corresponds to the N-acetyl methyl group and it is interesting to note that the indole C-7 proton is shifted downfield over 1 ppm to 8.3 ppm with respect to the N-unsubstituted compound due to the de-shielding effect of the N-acetyl function.

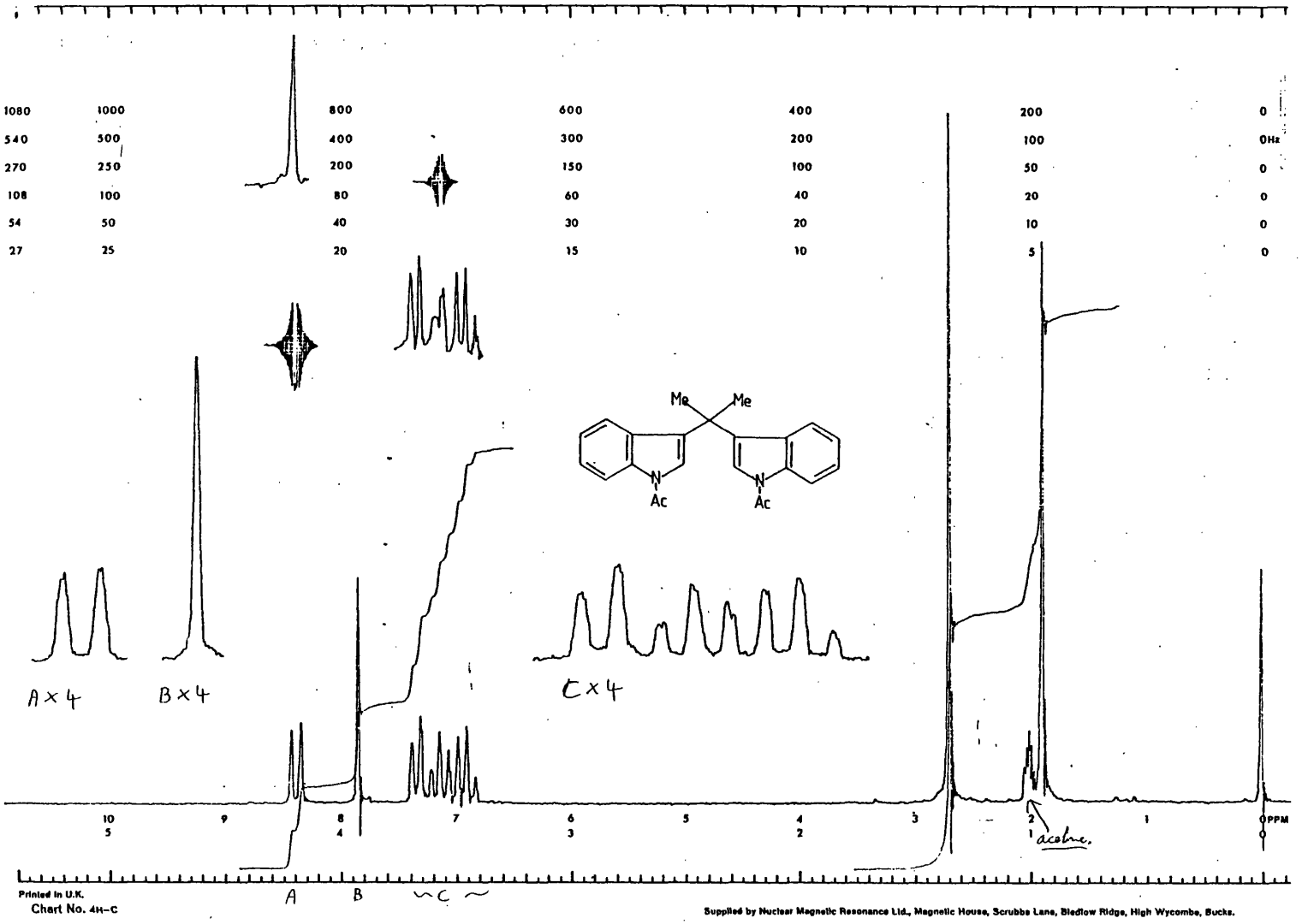
On one occasion we obtained a product from an ethanol recrystallization that melted at a temperature 50° higher than the expected product. Investigation of the spectral properties of this new compound confirmed the presence of an indole N-acetyl group.

Scheme 5



Route 18



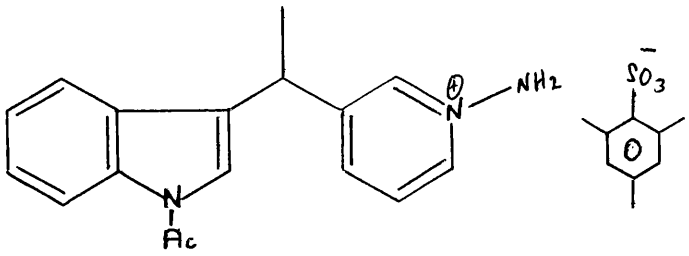


Printed in U.K.
Chart No. 4H-C

Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

The infra-red spectrum shows a strong absorption at 1700 cm^{-1} but we noted several differences from previous spectra. The pmr spectrum in deuteriochloroform indicated that there was no pyridine unit present. The spectrum consists of two singlets at 1.9 and 2.6 ppm, a complex signal centred at 7.2 ppm and a doublet (J=8Hz) at 8.4 ppm. The integral ratio is 3:3:4:1 and assuming the signal at 2.6 ppm is due to an N-acetyl group we conclude that the low field doublet is due to the adjacent benzenoid proton. In deuterioacetone the aromatic signals separate slightly and a decoupling experiment confirms that the doublet at 8.4 ppm is coupled to a signal at 7.1 ppm while the signal due to the indole α-proton is shifted downfield to 7.8 ppm and is shown as a sharp singlet. The mass spectrum of this compound shows a molecular ion at m/e 358 which suggests the structure is that of a symmetrical dimer (116). Elemental analysis results serve to support this formulation, the product being formed, we speculate, when acetone, present in the diethyl ether used as solvent during the original Grignard reaction, reactedto give the typical bis-indolyl product[54](117) which was subsequently acetylated to give (116) (Scheme 5). Unfortunately the contaminated solvent could not be traced so we were unable to confirm our belief.

Despite this diversion we were now ready to prepare (Route 18) O-mesitylsulphonylhydroxylamine (MSH)(80) required for amination of the indole (79,R=Ac). A solution of methyl cyanide and ethanol in anhydrous ether was treated with hydrogen chloride to give the imidate hydrochloride (118) as colourless prisms. The oxime (119) was obtained as an oil after treatment of (118) with potassium carbonate and hydroxylamine. Meanwhile mesitylene (120) and chlorosulphonic acid were reacted to give mesitylenesulphonyl chloride (121) which was

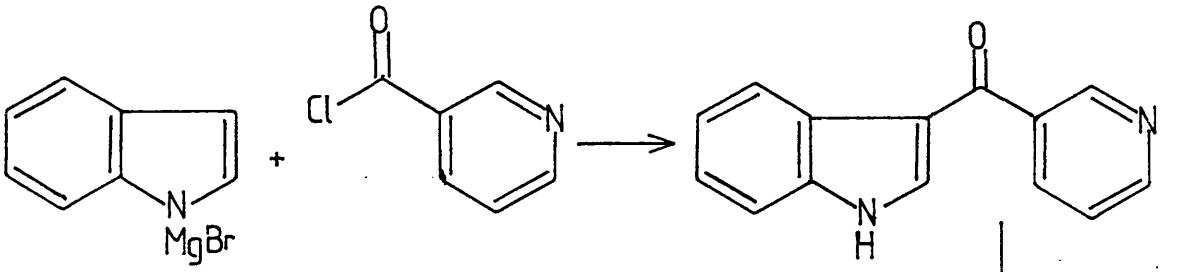


(123)

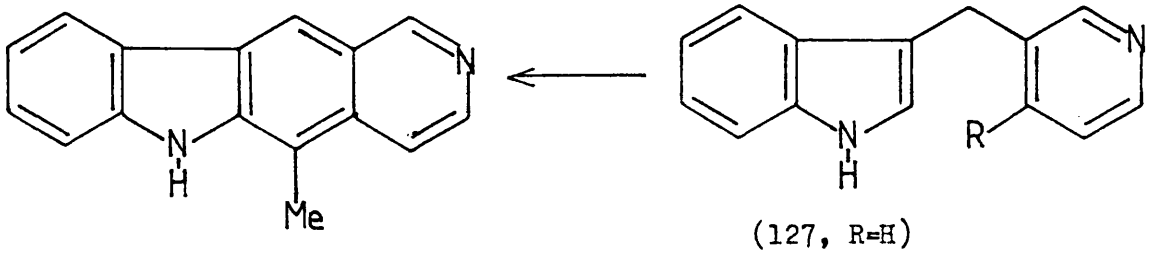
combined with (119) to give the precursor (122) as a white solid. This product when stirred with perchloric acid afforded MSH as a white, unstable solid. When warmed or left in air this compound is prone to sudden decomposition and is kept only when necessary. (Samples under nitrogen in a freezer can be kept for around 3 weeks before deterioration).

A solution of the indole (79,R=Ac) in dichloromethane at $0^{\circ}C$ was treated with one molecular equivalent of MSH to give, on work-up (123) as a clear gum. This material was acetylated directly with acetic anhydride and then heated with methyliodide to yield the salt (81) as a yellow, amorphous solid. Reaction with potassium cyanide under aqueous conditions gave a brown oil which was taken up in ethanol and irradiated with ultra-violet light. Elution of the crude material down a basic alumina column gave a small quantity of a brown oil which could not be induced to crystallize. The infra-red spectrum of this material displayed a small peak at 2235 cm^{-1}, which we assumed was due to C≡N stretching, while the mass spectrum showed the presence of a molecular ion peak at m/e 247. TLC analysis showed a long smear on a variety of supports in several solvent systems. The presence of a chiral centre in the nitrile (82) plus restricted rotation about the bridging ethyl group may explain the difficulties we encountered in isolating the compound as a crystalline solid. The pmr spectrum was not entirely satisfactory and elevated temperature experiments were uninformative. However this compound is not new[28] and a comparison with an authentic sample suggested that we had obtained the desired product contaminated with some unknown material. We decided to proceed at this stage and the oil was heated with dilute alkali in an attempt to hydrolyse the cyanide function. The product we obtained from this reaction appeared to be unchanged starting

material but when dilute mineral acid was employed work-up afforded a dark gum which showed no evidence of a C≡N stretching absorption in the infra-red spectrum. TLC analysis showed the presence of several fluorescent components and we were able to isolate several of these by column chromatography. The amounts we obtained, however, did not enable us to characterise these products. These brief investigations exhausted our supply of the nitrile (82) and with the attendant problems in preparing the starting pyridoindole (79) we decided to switch our attentions to a more accessible model.

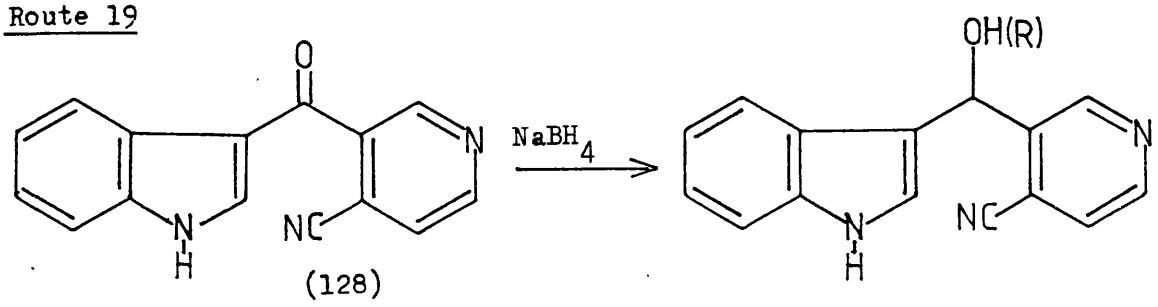


(125) (126)

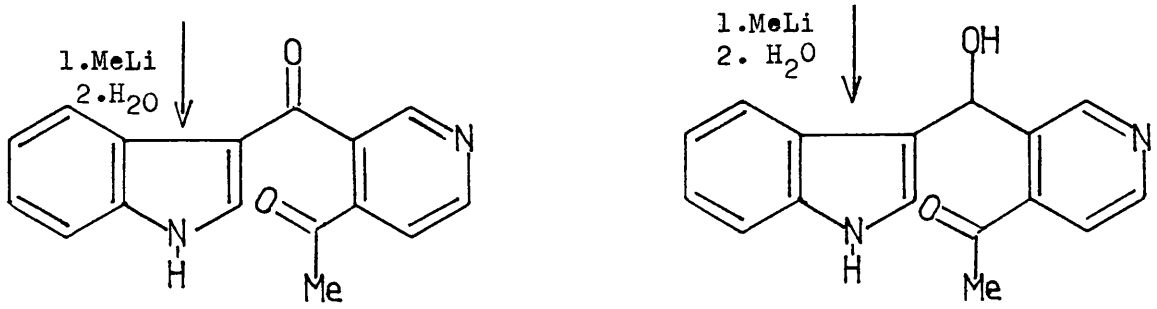


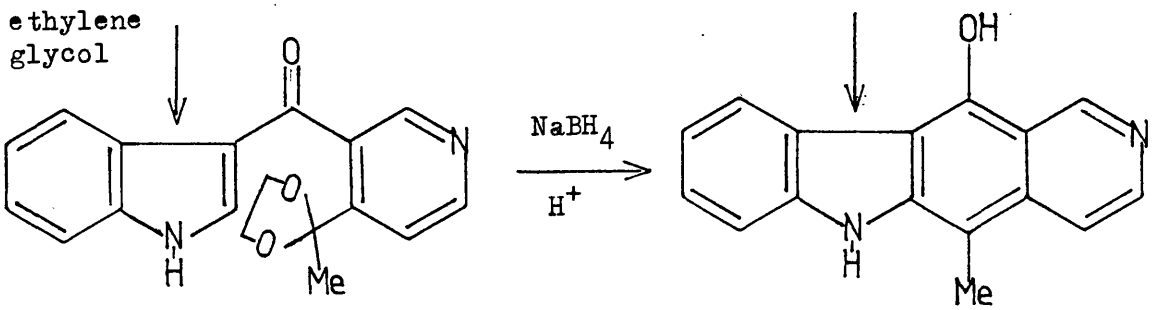
(127, R=H)
(132, R=CN)

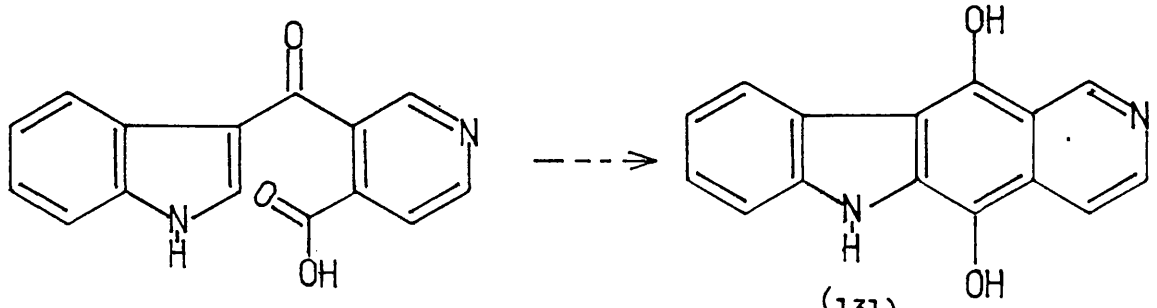
Route 19



(128)







(130) (131)

Synthetic efforts from 3-Nicotinoylindole

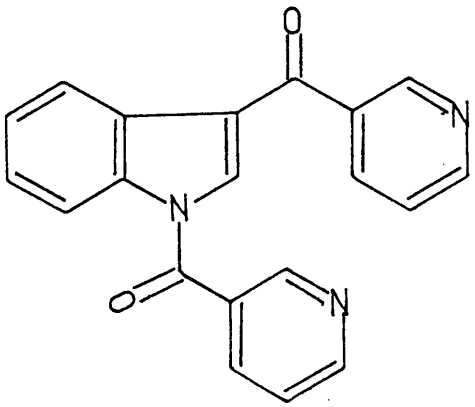
It has been shown[55] that 3-nicotinoylindole (126) is obtained in modest yield (25%) from the reaction of indolylmagnesium bromide and nicotinoyl chloride (125). Reduction of this carbonyl compound gives the methylene bridged analogue (127) from which 11-demethylellipticine has been synthesised[28]. Additionally the vinylogous amide allows other synthetic possibilities; thus we hoped to prepare a sufficient quantity of the 4-carbonitrile (128) to enable us to fully investigate conditions necessary for hydrolysis of the cyanide funtion. We also visualised several possible routes to 11-hydroxy or 11-alkoxyellipticine derivatives as summarised in Route 19.

The success of these schemes depends on the lability of the hydroxyl group attached to the methylene bridging unit and we anticipated having to modify this function to prevent dehydration occurring. We also entertained, albeit tenuously, the hope that the corresponding 4-carboxylic acid (130) would lend itself to an intramolecular cyclisation reaction leading ultimately to 5,11-dihydroxy-6H-pyrido(4,3-b)carbazole (131).

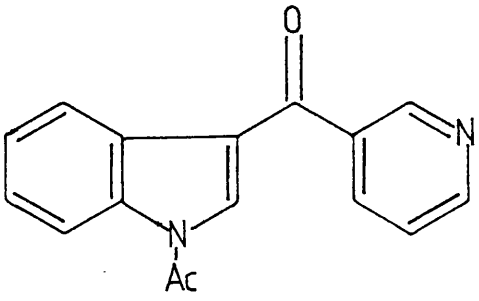
We considered that the reduced nitrile (132) would provide a readily accessible model if reactions involving the amide (126) proved disappointing.

Preparation of 1-(N-Acetyl-N-methylamino)-3-(1-acetyl-3-indolylformyl) pyridinium iodide (138)

Since the yield of product from the reaction of indolyl magnesium bromide with nicotinoyl chloride is not good we first investigated methods of improving the efficiency of this step. We suspected that the customary preparation of the unstable acid chloride used in this laboratory might not be entirely satisfactory. Previously nicotinic acid was treated with thionyl chloride to give the hydrochloride



(133)

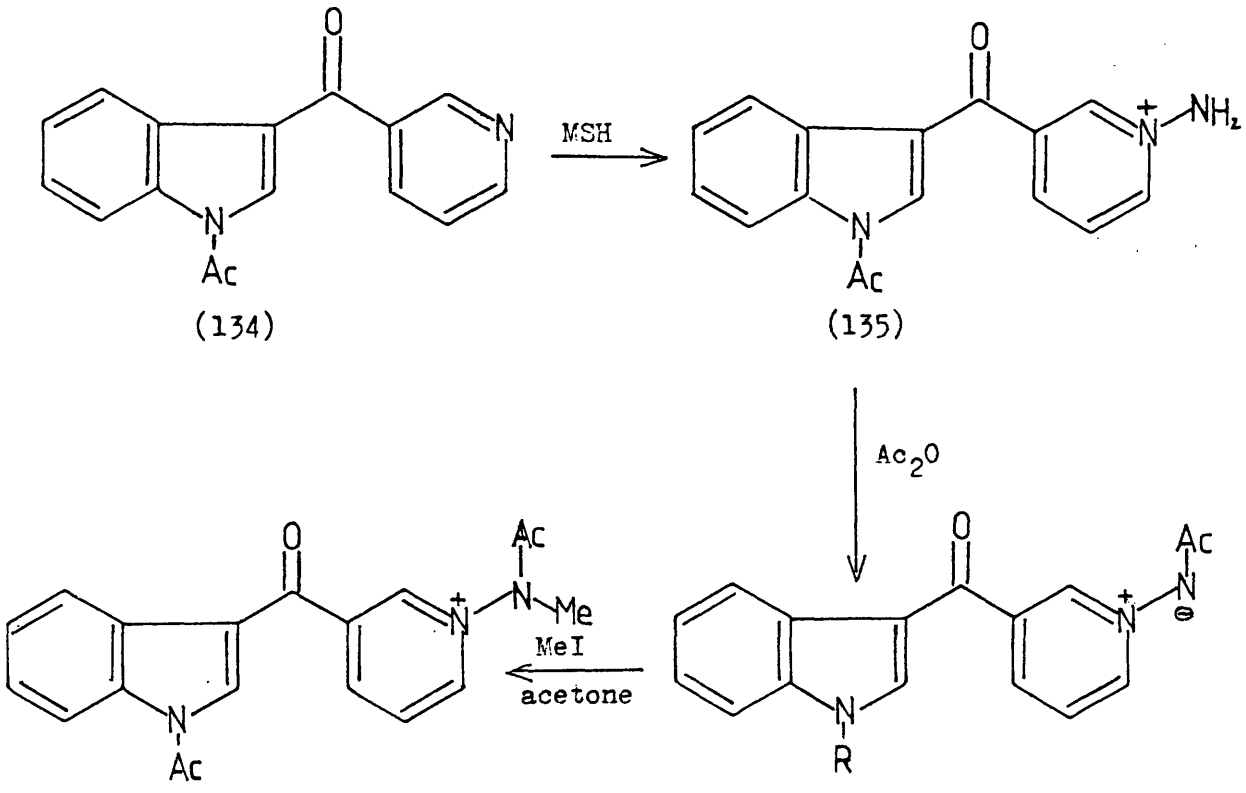


(134)

salt which was stirred for several hours with triethylamine to give the free acid chloride. We decided to use the method of Wingfield and co-workers[56] in which potassium nicotinate is treated with oxalyl chloride in dry benzene to give a solution of the free acid chloride directly, in yields of 80% or better. Since the by-products of the reaction are carbon monoxide, carbon dioxide and potassium chloride filtration, (if necessary), gives an anydrous solution ready for further reaction. Using these solutions for reaction with the indole Grignard reagent at -10°C we obtained 3-nicotinoylindole in yields of 65-75%. At higher temperatures we obtained evidence from mass spectral data suggesting that the product was contaminated with a compound containing two nicotinoyl-units. An extra molecular ion peak at m/e 327, coupled with loss of 106 mass units corresponding to fragmentation of the N-nicotinoyl unit, was indicative we felt, of the compound (133). Attempts to separate this compound from the reaction products by crystallization or by chromatography failed, probably due to the ease with which this type of compound deacylates.

3-Nicotinoylindole was obtained as colourless prisms, after several recrystallizations from ethanol, and its ultra-violet spectra is compatible with the extended conjugation present in the molecule, showing maxima at 240, 258, 270 and 310 nm. The carbonyl absorption in the infra-red spectrum is at 1600 cm^{-1}, a manifestation of the compounds vinylogous amide nature. The pmr spectrum includes a broad singlet at 12.1 ppm corresponding to the indole N-H proton while the pyridine protons adjacent to nitrogen appear as a finely split doublet (J=1Hz) and a double doublet (J=1Hz and J=5Hz) at 9.0 and 8.8 ppm respectively, the signal at lower field being due to the C-2 proton.

Indole N-acetylation was effected by heating with acetic anhydride to give the product (134) which exhibits two carbonyl bands



(134) (135)

(136, R=Ac)
(137, R=H)

(138)

Table 4

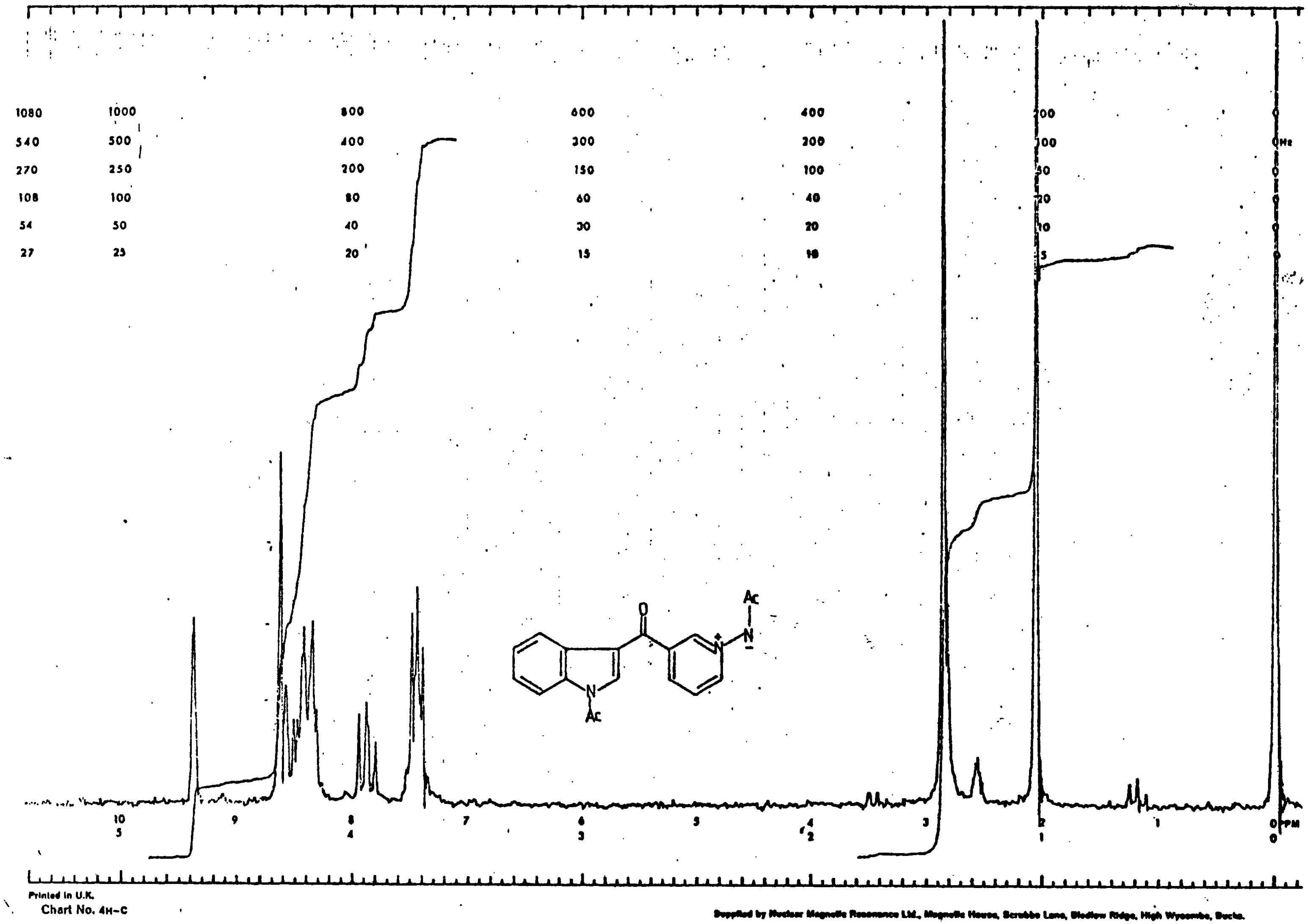
	COMPOUND		
	(135)	(136)	(138)
I.R.(cm^{-1})	1730 (C=O,N-Ac) 1640 (C=O,bridge)	1720 (C=O,N-Ac) 1650 (C=O,bridge) 1560 (C=O,$\bar{N}$-Ac)	1720(C=O,N-Ac) 1695(C=O,$\overset{+}{N}$-N-Ac) 1650(C=O,bridge)
solvent	d^6DMSO	$CDCl_3$	d^6DMSO
1H nmr (ppm)	3H,s,2.2 (p-Me) 6H,s,2.5 (o-Mex2) 3H,s,2.8 (N-Ac) 2H,s,6.8 (benzenoid protons) 2H,bs,8.5 (NH)	3H,s,2.1 ($\overset{+}{N}$-$\bar{N}$-Ac) 3H,s,2.9 (N-Ac) 1H,s,9.4 (H-2)	3H,s,2.2 ($\overset{+}{N}$-N-Ac) 3H,s,2.8 (N-Ac) 3H,s,3.9 (N-Me) 1H,s,10.0 (H-2) 1H,d,9.7 (H-6) 1H,d,9.3 (H-4)

in the infra-red spectrum. That due to the N-acetyl function appears at 1725 cm^{-1} while the bridging carbonyl unit is shifted to 1625 cm^{-1} indicating that the indole nitrogen lone pair of electrons are less available to conjugate with this latter carbonyl function. The ultra-violet spectrum also displays this property with the extinction coefficient of the λ310 nm maxima being greatly reduced. The pmr spectrum shows a three-proton singlet at 2.65 ppm, a resonance typically due to the protons of a N-acetyl unit.

Amination of this compound with MSH gave a quantitative yield of the salt (135) as a white solid instead of a gum, which is more usual for this type of compound. We found that modifications of subsequent steps in the sequence were necessary since, for example, acetylation of the salt (135) under aqueous conditions gave the indole N-H analogue of (136) ie (137). By acetylating (135) as a slurry in chloroform and neutralising the excess acetic anhydride quickly the diacetyl compound was obtained in good yield. It was found advantageous to retain the indole N-acetyl function since reaction of this substrate with methyl iodide gives a much cleaner product than does reaction of the corresponding N-H compound.

When we attempted to methylate the zwitterion (136) by heating in methyl iodide we obtained only the deacetylated product (137). However when the reaction was repeated using a mixture of acetone and the alkyl iodide the metho salt (138) separated as a bright yellow solid. We were able to isolate all the compounds in this series as solids which allowed study of their spectral characteristics in detail. The salient features of these spectra are shown in Table 4.

The pmr spectrum of the salt (135) clearly displays the signals associated with the protons of the anion while those corresponding to the cation include two broadened resonances which can


1080 540 270 108 54 27
1000 500 250 100 50 25
800 400 200 80 40 20
600 300 150 60 30 15
400 200 100 40 20 10
200 100 50 20 10 5
0 Hz
Ac
N
Ac
O
10 5
9
8 4
7
6 3
5
4 2
3
2 1
1
0 0 PPM
Printed in U.K.
Chart No. 4H-C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

be removed by deuteration.

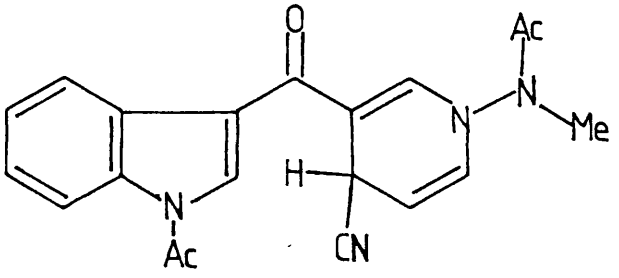
The diacetyl compound (136), obtained as colourless needles from chloroform, displays the protons of the $\overset{+}{N}$-$\overset{-}{N}$-$COCH_3$ group at a relatively high field position of 2.1 ppm. Clearly the di-ionic structure has a strong shielding effect on the methyl protons. It is also interesting to note that one of the α-pyridine protons is shifted downfield to resonate at 9.4 ppm. It seems likely that the origin of this signal is the proton which is sandwiched between the pyridine nitrogen atom and the bridging carbonyl group.

The pmr spectrum of the metho salt (138) exhibits three, three proton singlets at 3.9, 2.8 and 2.2 ppm corresponding to the resonances of the protons of the $\overset{+}{N}$-N-CH_3, N-$COCH_3$ and $\overset{+}{N}$-N-$COCH_3$ groups respectively.

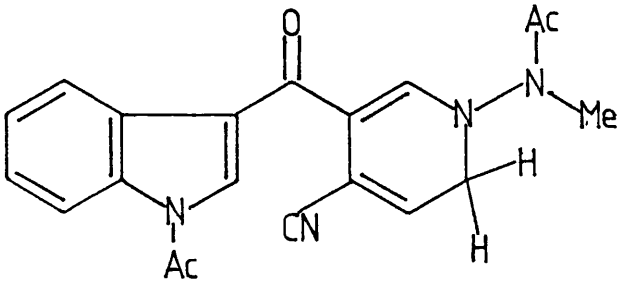
Reaction of the Metho salt (138) with cyanide ion.

The salt (138) proved to be almost insoluble in water and initial reactions between this compound and potassium cyanide were conducted either in ethanolic solution or with the salt as a dispersion in water. In either case ammonium chloride and potassium cyanide were added as aqueous solutions. Under aqueous conditions a gum was soon deposited and when this was extracted into chloroform and the solvent evaporated the residue turned from yellow to green and then back to yellow again on standing. Reactions in ethanolic solution also underwent this colour change which we initially assumed was due to nucleophilic attack by CN^- at the pyridinium γ-position, giving a dihydro system, followed by rearomatisation under the influence of the ultra-violet radiation in sunlight.

A pale yellow solid was obtained from these residues by dissolving them in ethanol and allowing the resulting solutions to stand overnight. This solid, in the infra-red spectrum, displays

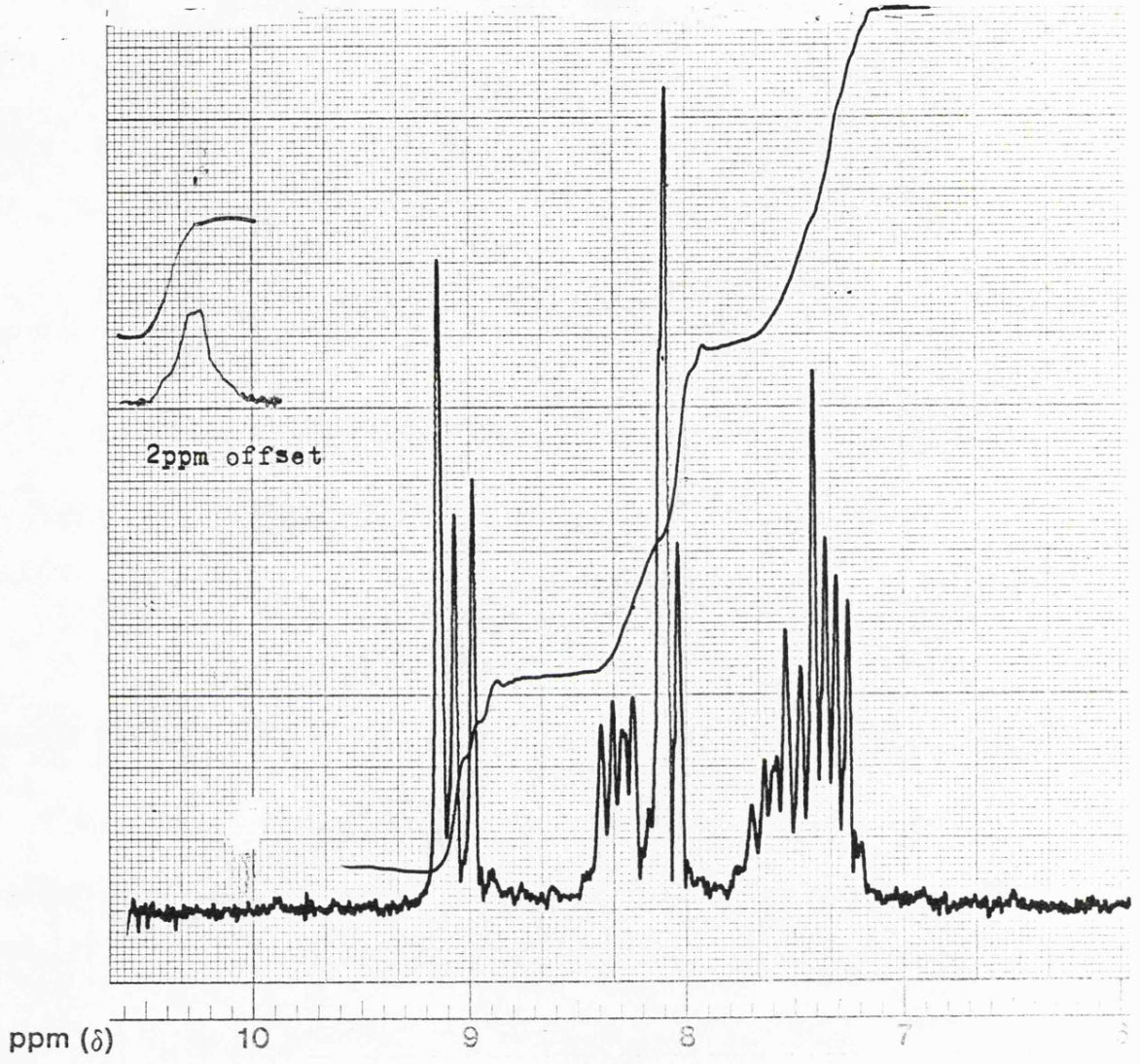


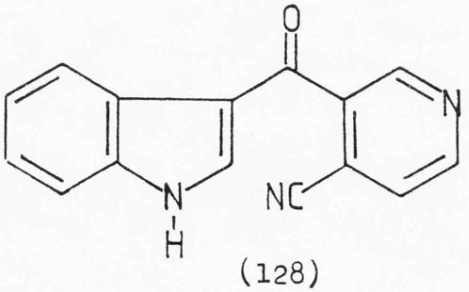
(139)



(140)

three carbonyl absorptions at 1720, 1685 and 1600 cm^{-1} while there is a small band at 2230 cm^{-1} due to C≡N stretching. From this evidence we concluded that we had isolated a dihydro intermediate. The pmr spectrum shows three, two proton multiplets at δ 8.3, 7.9 and 7.35 ppm while single proton multiplets occur at δ 6.6, 5.2 and 4.7 ppm. There are three sets of signals due to methyl group resonances at δ 3.2, 2.7 and 2.0 ppm and apart from the δ 2.7 resonance these last signals are not singlets but two-line systems with separations not reflected elsewhere in the spectrum. Spin-spin interactions do not apply and we suspect diastereoisomerism since this has been a feature of structures in this series. Unfortunately this product is unstable and may not be subjected to variable temperature pmr spectroscopy so that this duplication at signals makes the interpretation of the spectrum difficult. However a comparison of chemical shift data obtained by other workers points strongly to the structural assignment (139) rather than the alternative (140). The spectrum does not show any evidence of the relatively large coupling constant expected for the signals of the geminal protons of the structure (140). A close inspection shows the resonance at δ 6.6 ppm to consist of two broad overlapping doublets ($\underline{J}$=9Hz) arising from coupling of C_5-H with C_4-H and/or C_2-H. Attempts to purify this compound by recrystallisation were unsatisfactory and we resorted to column chromatography on neutral alumina. Elution with diethyl ether yielded trace amounts of a purple fluorescent material. When the polarity of the solvent system was increased (1-5% methanol in ether) pale yellow prisms were obtained. The infra-red spectrum of this new compound shows N-H stretching at 3200 cm^{-1}, a band due to C≡N stretching at 2220 cm^{-1} and one carbonyl absorption at 1620 cm^{-1} corresponding to the bridging unit. From this data we concluded that passage down the column caused the aromatisation of the pyridine ring with loss of the amino protecting function as





(128)

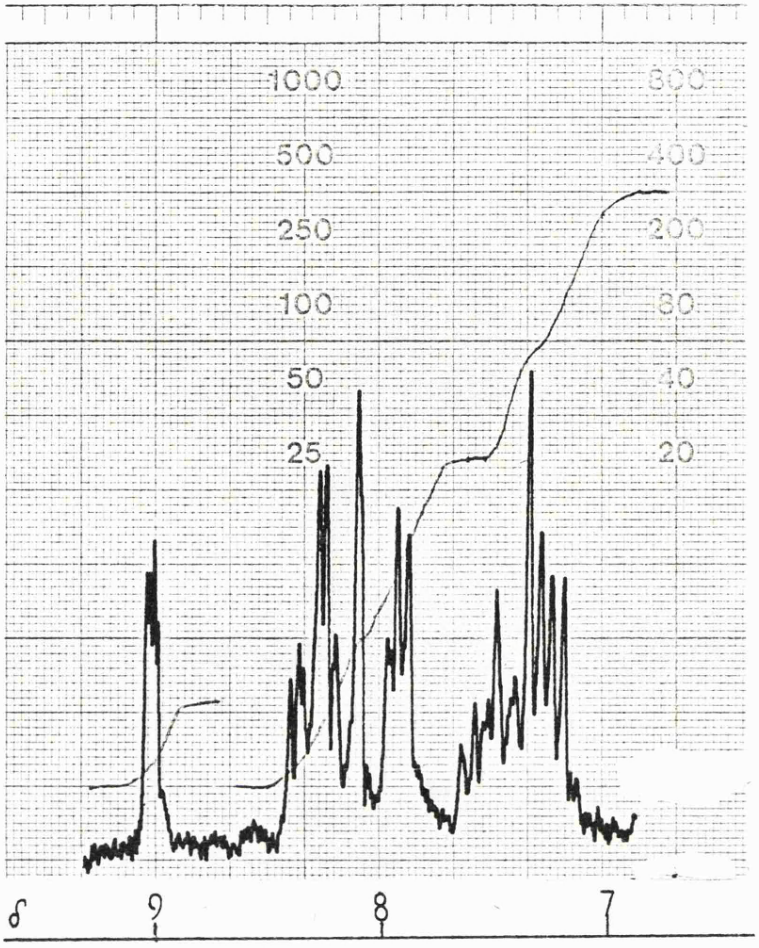
methylacetamide. De-acylation of the indole nitrogen also occurs yielding the nitrile (128). The mass spectrum shows a molecular ion peak at m/e 247 while the pmr spectrum in d^6DMSO shows only aromatic signals with the N-H absorption at lowest field. The rest of this spectrum may be analysed in some detail. Proton H-2 absorbs as a sharp singlet at 9.2 ppm adjacent to a doublet (J=5Hz) due to the H-6 proton at 9.1 ppm. The remaining pyridine proton appears as a doublet (J=5Hz) at 8.1 ppm. A one proton singlet at 8.1 ppm corresponds to the indole-2-H while the resonance due to the indole 4-proton appears shifted downfield from the other indolic absorption at 8.3 ppm due to "long-range" interaction with the carbonyl group. The remaining protons appear as a three proton complex signal centred at 7.4 ppm.

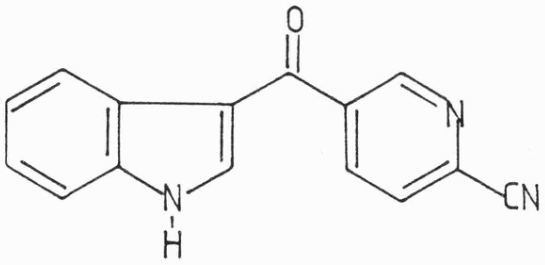
Subsequent experiments showed that aromatisation could be effected by warming the dihydro compound in ethanol and allowing the resulting solution to stand for a day whereupon crystals of the fully aromatic nitrile separated. That this latter compound is substituted in the γ-position of the pyridine ring is confirmed by the pmr spectrum since even at 100 MHz it shows no evidence of the fine meta-splitting one would expect in alternate structures. However, we also isolated, in minute amounts, another product from these columns which we suspected, but were not able to prove, was an α-substituted analogue of (128).

Having isolated the desired, pure carbonitrile we set about determining conditions for hydrolysis. Refluxing in dilute mineral acids returned only starting material but when the nitrile was heated with 50% sulphuric acid for two hours under an inert atmosphere we obtained a dark red solution which when neutralised gave a white precipitate. Attempts to crystallise this material were not successful and we had to handle this product as an amorphous solid. The infra-red spectrum showed a band at 2230 cm^{-1} suggesting the presence of starting material but there was also a small absorption at 1695 cm^{-1} which we felt might be indicative of an amidic or acidic carbonyl group.

The mass spectrum showed the presence of a molecular ion at m/e 266 which corresponds the expected mass of the acid (130). The pmr spectrum did not provide any conclusive evidence since the trace was very similar to that of the starting material. TLC analysis on silica indicated that there were two main spots, one of which had the same Rf value as the nitrile (128). We concluded that partial hydrolysis had occurred and modified the reaction conditions in an attempt to improve the yield of the acid. However increased reaction times or the use of more concentrated acid solutions gave large amounts of charred material which could not be characterised. Separation attempts were also unsatisfactory and we eventually turned our attention to the use of alkaline conditions for the desired hydrolysis. Heating with dilute caustic soda yielded impure starting material but when ethylene glycol was used as a solvent the initially yellow sdution darkened and then, after a further half an hour, became orange in colour. Work-up gave a small quantity of an orange gum which was shown to consist of many components by TLC. One of these components had a Rf value indentical to that of the presumed acid isolated from the reaction employing 50% sulphuric acid. Once again it appeared that hydrolysis was only partial and we were unable to isolate any pure material from these reactions despite varying the conditions. Since pyridine carboxylic acids are relatively easy to decarboxylate it is perhaps likely that the severe conditions we had to employ to achieve any hydrolysis at all served also to bring about this undesirable course.

At this point our stock of the nitrile (128) was exhausted and since we were obliged to prepare additional amounts we decided to vary the conditions of the cyanide addition reaction to see if we could improve the yield. On one occasion the metho salt (138) was

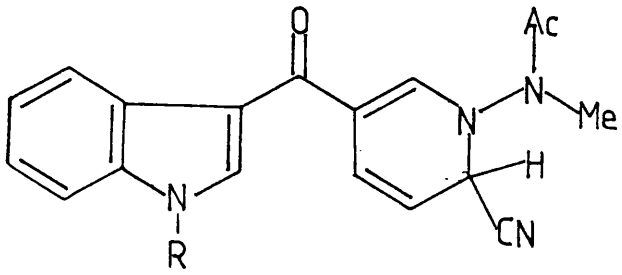




(141)

dispersed in chloroform while an aqueous solution of ammonium chloride and potassium cyanide was added with vigorous stirring. After an hour the solid had dissolved and the organic layer was separated, washed well with water and evaporated to yield a yellow gum. This product was taken up in ethanol and irradiated to yield, on standing, a pale yellow solid. A cursory glance at the infra-red spectrum of this material indicated that it was fully aromatic but we were surprised when the pmr spectrum differed from that of the expected nitrile (128). Instead of the singlet low-field peak due to H-2 of the pyridine unit there now appears a finely split signal ($\underline{J}$=1Hz). A multiplet at δ 8.2 ppm corresponds to four protons while the rest of the spectrum consists of an N-H absorption and a three proton multiplet at 7.4 ppm. A closer look at the infra-red spectrum shows that there are differences in the finger-print region and we realised that we had obtained the 2-cyanopyridine (141). A comparison on TLC plates confirmed that this compound was one of the minor products obtained during the preparation of the 4-cyanopyridine (128). The resonances at 8.2 ppm are thus due to the pyridine protons H-4 and H-5 and the indole H-2 and H-4 protons. Deuteration of the sample removes the indole N-H resonance and simplifies one of the signals at 8.2 ppm since the indole α-hydrogen now gives rise to a sharp singlet, which is clearly visible rising above the other peaks. The fine splitting of the signal at lowest field (pyridine H-2) is due to the presence of the meta proton at the 4-position of the pyridine ring.

It has been generally assumed, but not proved, that the size of the pyridine N-substituent is the deciding factor in determining whether α-substitution becomes a significant reaction. The findings above suggest that the state of solvation around the respective anion and cation may also be critical.



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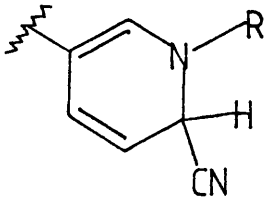

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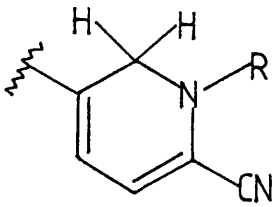
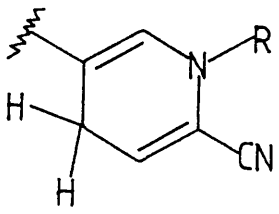


(143)



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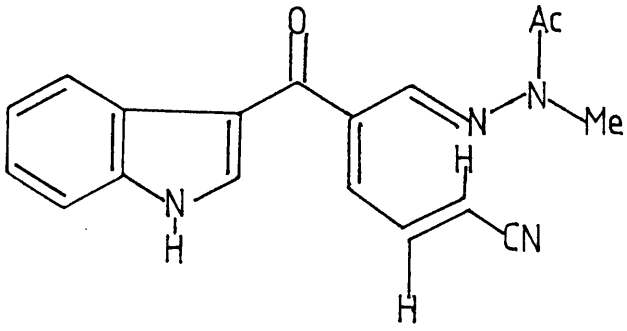
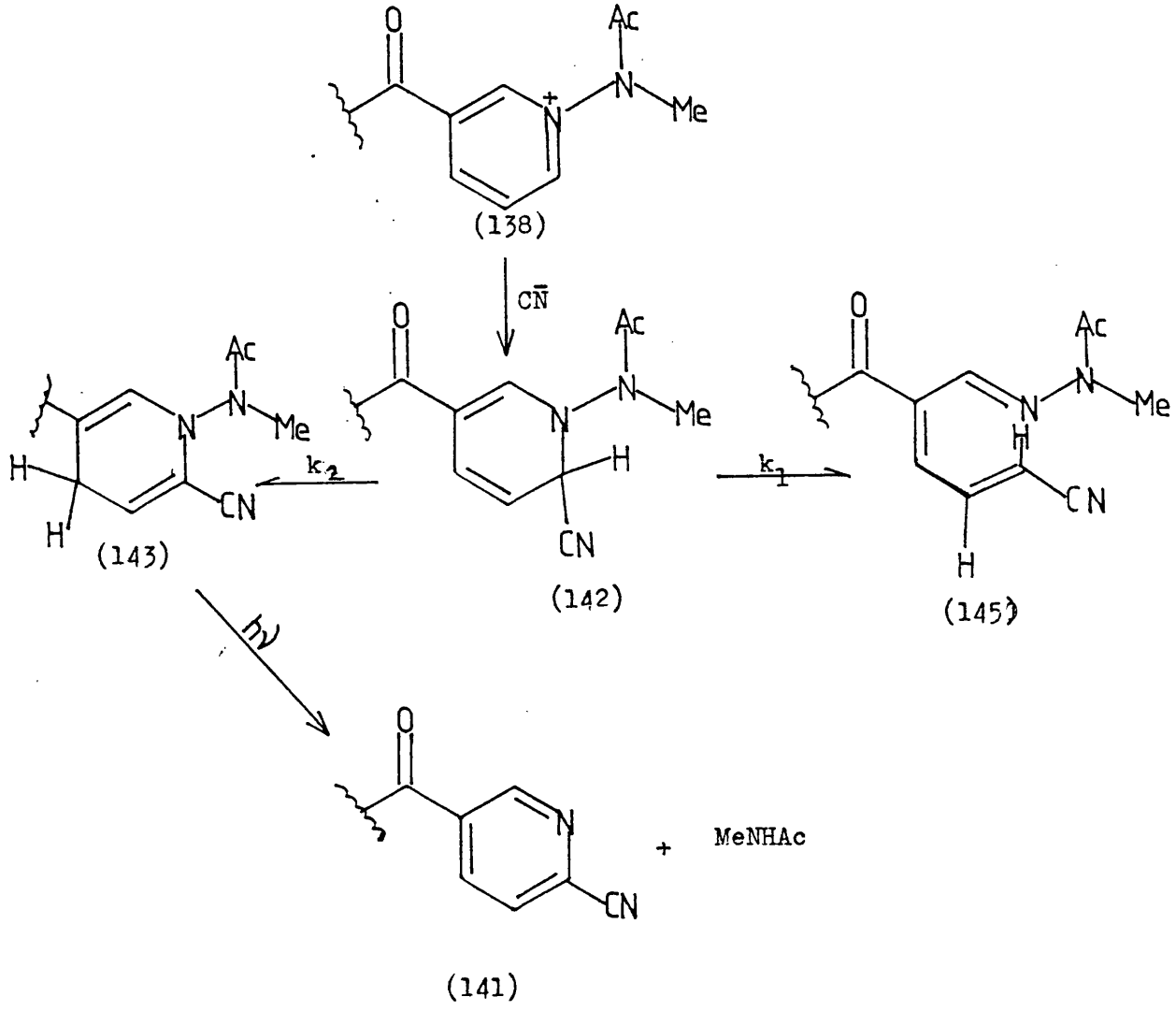


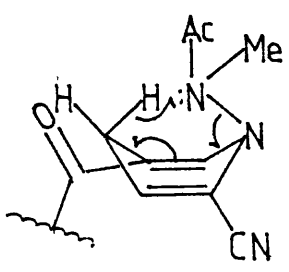
(145)

We next set out to isolate the corresponding 2-cyanodihydropyridine (142) and the procedure for the cyanide addition was repeated with the reaction flask enveloped in aluminium foil. Work-up yielded a pale yellow solid which in the infra-red spectrum shows a strong absorption at 3200 cm^{-1} corresponding to N-H stretching. There are also intense bands at 1695 and 1600 cm^{-1} due to the acetyl function of the amino protecting group and the bridging carbonyl unit respectively. The pmr spectrum displays two, three-proton singlets at 2.2 and 3.2 ppm due to the methyl and acetyl group hydrogen atoms while a low field, broadened singlet at 12.4 ppm is clearly indicative of an indole N-H resonance. The analysis of the rest of the spectrum is not so straightforward however. There is a one proton singlet at 8.3 ppm superimposed upon a complex one-proton signal. A doublet (J=9Hz) at 7.9 ppm is due to a single proton and is coupled to a one proton, four line pattern centred at 6.7 ppm (double doublet; J=16.5Hz). Between these sets of signals is a one proton multiplet at 7.5 ppm and a three proton multiplet at 7.3 ppm. Decoupling experiments indicate that the proton causing the further coupling of the 6.7 ppm system lies in this latter multiplet. Finally, there is a sharp, one proton singlet at 6.2 ppm.

From this data it seemed apparent that we had isolated a related intermediate to that involved in γ-substitution but none of the three possible structures (142), (143) or (144) can be reconciled with the pmr spectrum. For example although a 16.5Hz coupling constant is possible for the geminal protons in (143) or (144) the chemical shift positions dissuade us from these structures. The third arrangement (142) does not contain a trans orientated pair of protons about a double bond and the maximum value for proton spin-spin interactions within this structure as measured by coupling constant would be ~10Hz.

Scheme 20





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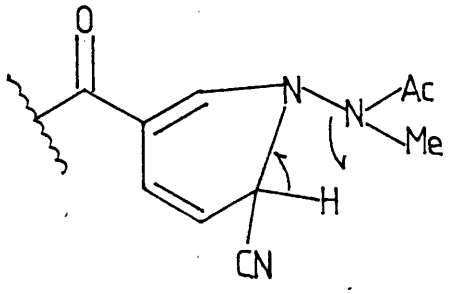
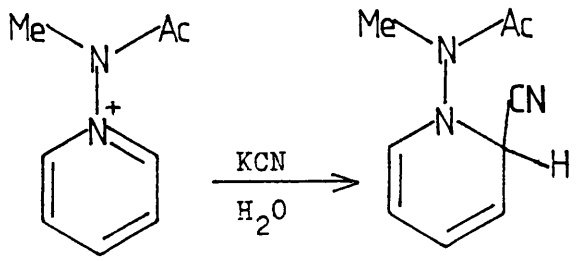
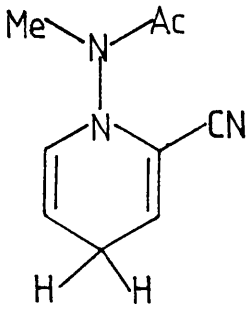


(142)

A consideration of all these factors leads us to believe that the structure consists of the ring-opened system (145) in which there is a trans, disubstituted double bond, one proton of which is further coupled to an olefinic or an aromatic proton. Attempts to cyclize the compound using photochemical means failed, indicated that this system is not normally the precursor to the α-cyanopyridine (141) and despite several attempts we were not able to isolate the α-cyanodihydropyridine (142) which should be the initial product of the addition of cyanide ion to the salt (138). If the triene (145) is not the precursor of the α-cyanopyridine in the normal photolysis experiment and the 2-cyano-1,2-dihydropyridine (142) is not present it suggests that the latter compound is readily converted into another compound which is then, in turn, converted to (141). (Scheme 20). The relative values of the rate constants k_1 and k_2 is then determined by the nature of the solvents employed. It seems possible that the photochemical degradation of the N-N bond is a concerted process in which case a 1,4-dihydropyridine e.g. (146) adopting a boat conformation is a much better substrate than the 1,2-dihydropyridine (142). Thus following this speculation through it may be that under the appropriate solvent conditions the initially formed 1,2-dihydropyridine undergoes prototropic change to the relatively stable isomeric 1,4-dihydro compound (143) which on subsequent photolysis affords the aromatic 2-cyanopyridine. The relative instability of (142) may be attributed to the size of the substituent groups and under less polar conditions it ring-opens rather than undergoing prototropic shift as previously required. The unknown intermediate therefore, is the 1,4-dihydro-2-cyanopyridine (143). Unfortunately, we are unable to offer tangible evidence for this scheme since no other compounds were isolated in a



(147) (148)



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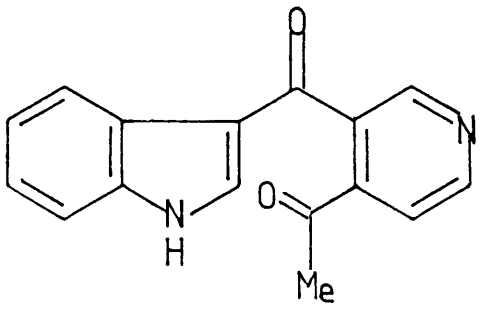
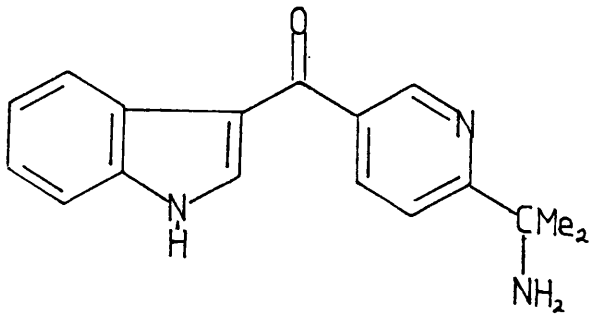


(151)

pure state. However, if our reasoning is correct, it seems probable that the 2-cyano-1,2-dihydropyridine (148) claimed by Okamoto *et al*[58,59] as the product from the addition of cyanide ion to the salt (147) has the wrong structure and should be reformulated as the 1,4-dihydro compound (149). These Japanese workers found that electron-withdrawing substituents in the 3-position of thepyridinium ring promote 2-substitution and that reactions performed under wholly aqueous conditions give rise to 4-substitution whereas when less polar solvent systems are employed considerable quantities of the 2-substituted products are isolated. Our results are in agreement with these findings and it is apparent that it is possible, by altering the solvent system, to allow 2-substitution to become the major process. Sammes and Katritsky report[60] that the concentration of cyanide ion in contact with the pyridinium cation is of paramount importance in determining the position of nucleophilic attack. High concentrations favour 2-substition while low cyanide ion concentration allows preferential attack at the 4-position. These findings are in direct contradiction of the Okamoto group and our evidence, circumstantial as it is, seems to support the Japanese workers' conclusions.

Since our investigations led us to obtain a substantial quantity of the 2-cyanopyridine (141) we decided to employ this substrate in our hydrolysis experiments since any influence exerted by the bridging carbonyl group would be reduced. Once again, however, mild basic and acid hydrolysis attempts failed and we decided to vary our approach slightly. We considered that the cyanide function in (128) should react with methyl lithium, giving the imine, and that subsequent hydrolysis would furnish the corresponding 4-acetyl derivative (151). With this derivative we hoped to either find conditions to effect cyclisation directly or to protect the acetyl carbonyl group, reduce



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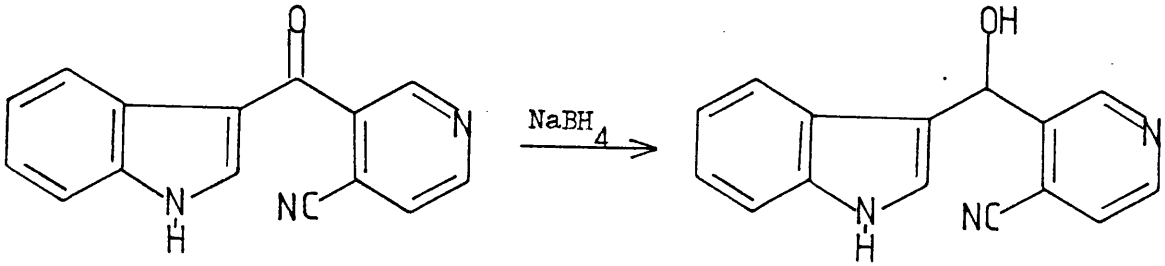


(128)

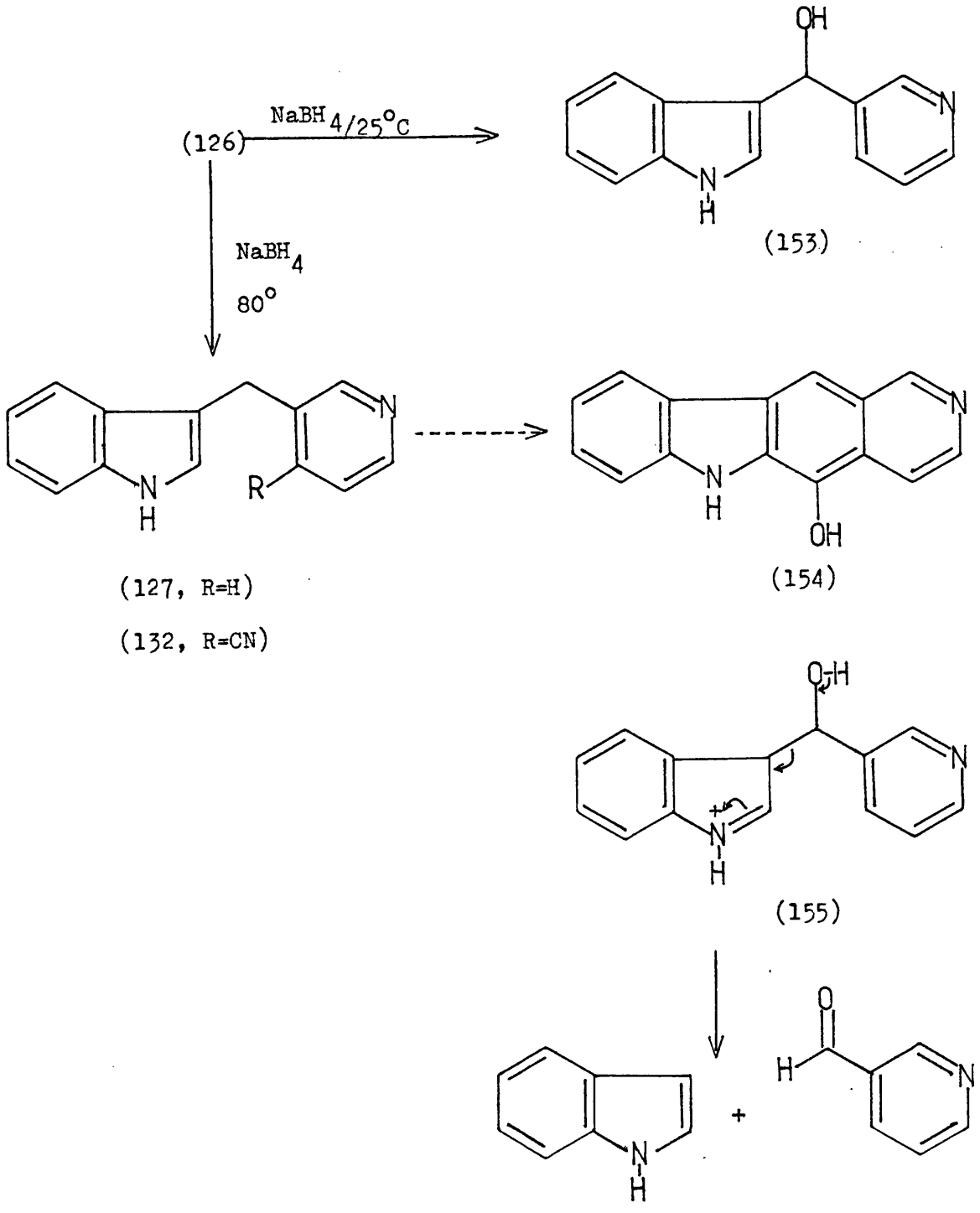
(153)

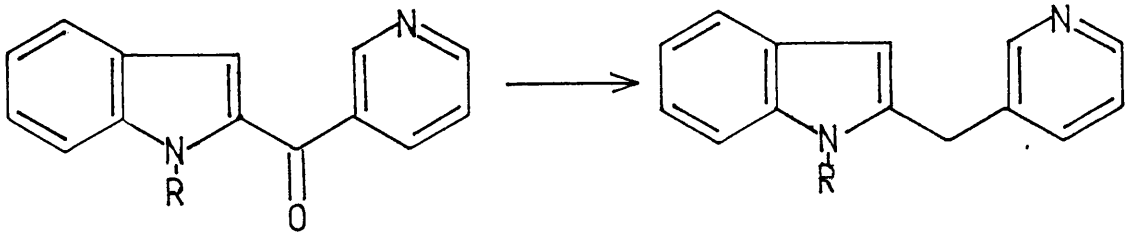
the bridging carbonyl function and then ring-close the resulting alcohol to give 11-hydroxyellipticine. However, treatment of (128) or (141) with a three molar excess of methyl lithium at -10°C returned only the starting nitriles. On one occasion when the nitrile (141) was reacted under more severe conditions(a 10 molar excess of methyl lithium at 0°C) an intractible product was obtained which we found difficult to purify but from which an orange oil was obtained which appeared, by pmr, to contain the amino-compound (152). A broadened, singlet absorption corresponding to six protons appeared at δ 2.9 ppm while a rather indistinct signal, presumably due to the resonance of the N-H protons, was shown at δ 4.0 ppm. Despite varying the conditions we were unable to obtain the desired imine from these reaction mixtures and treatment of the crude products with 20% acetic acid proved unproductive since only black tars were isolated.

We next tried an approach from the alcohol (153) which was obtained from the carbonyl compound (128) after treatment with sodium borohydride in ethanol at room temperature. The product from this reaction was a pale brown oil which was shown, by TLC, to contain one major component. Column chromatography afforded a similar pale oil which showed only one spot on TLC. This material could not be induced to crystallize and the spectral data we obtained was not entirely satisfactory since the pmr spectrum contained many broad peaks. In the infra-red spectrum there was a broad absorption at 3100 cm^{-1} with a small band at 2225 cm^{-1} while a molecular ion peak at m/e 249 was shown in the mass spectrum. This 'crude' product was treated with methyl lithium as before to yield an orange gum which was warmed, on a steam-bath, with 20% acetic acid for 30 minutes. Work-up afforded a dark brown oil which was shown, by TLC analysis, to be a complex mixture. There was no sign of a C≡N stretching absorption in the infra-red spectrum but unfortunately we were unable to

to characterize the oil further.

The apparent lack of reactivity of the nitrile function under these conditions was both a puzzle and a disappointment to us. It appeared as if the bridging carbonyl unit was exerting some profound effect which was preventing reaction occurring except under severe conditions when presumably further disruption of the substrate occurred. Before abandoning this approach we considered that it would be worthwhile synthesising the corresponding methylene bridged analogue (132) and repeating several of the procedures described above since any influence exerted by the carbonyl unit would be absent and reactions might prove more expeditous.





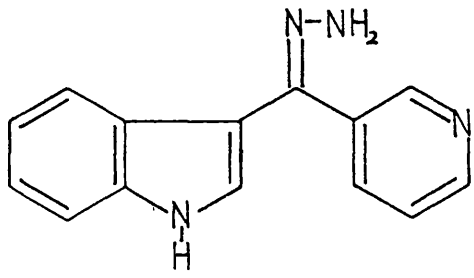
(156)

Synthetic approaches from Indol-3-yl 3-Pyridylmethane (127)

The reduction of 3-nicotinoylindole (126) in ethanol with sodium borohydride gives two distinct products, at 25°C the alcohol (153) is obtained whereas in refluxing ethanol the fully reduced compound (127) is isolated[25]. Previous work[61] has shown that at temperatures between this reaction affords large amounts of a gum. From (127) we sought to prepare sufficient quantities of the corresponding 4-cyanopyridine (132) and to profitably hydrolyse this derivative. We then hoped to determine conditions necessary for the cyclisation of the product acid to yield 5-hydroxy-11-demethylellipticine (154).

Large scale reductions of 3-nicotinoylindole using sodium borohydride in boiling ethanol proved disappointing in that the desired product was always contaminated with several impurities. TLC analysis demonstrated the presence of 3 main components and when the crude product was subjected to column chromatography on silica we obtained substantial quantities of indole when the eluant was diethyl ether. Elution with chloroform gave (127) and when the polarity of the solvent was increased we obtained an intractable red gum. We were surprised to isolate indole from this reaction since it suggests that a retro-aldol reaction takes place from the imminium ion (155). Such a species could result from β-protonation of the indole alcohol but no sign of an appropriate pyridine derivative was found.

At this point we decided to investigate the possibility of utilising a Wolff-Kishner reduction on the amidic ketone (126) since Sundberg *et al* have successfully employed this method to reduce 2-substituted carboxyindoles ofthe type(156)[62,63]. We were guarded in our optimism since we appreciated that these compounds are less amide like than our own substrate and we were thus pleasantly surprised when a preliminary reaction between the amide (126) and hydrazine furnished



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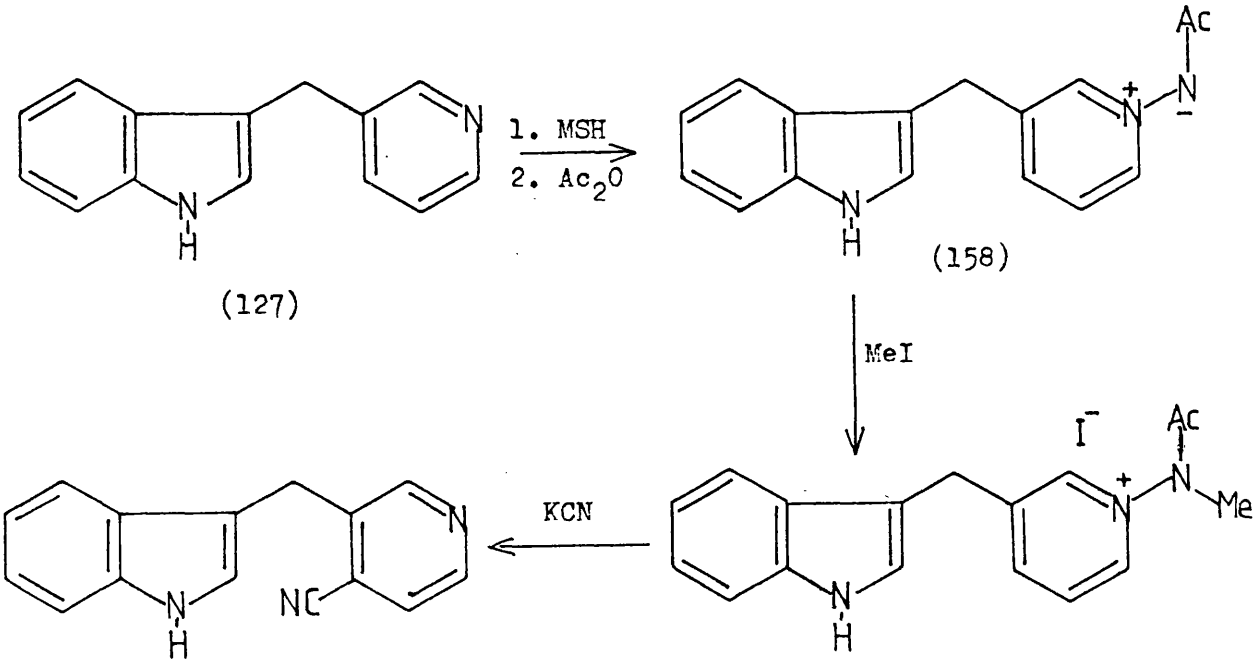
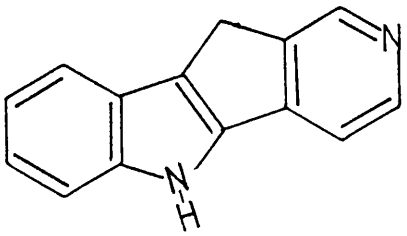


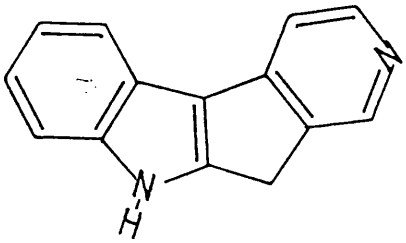
(127) (158) (159) (132)

the hydrazone (157) in good yield as a purple solid. The infra-red spectrum of this product displays two sharp N-H stretching absorptions at 3440 and 3350 cm^{-1} with the indole N-H stretch at 3140 cm^{-1}. Using full Wolff-Kishner conditions we obtained the picolyl derivative (127) in 75-80% yield. The infra-red spectrum is devoid of any carbonyl absorptions while the pmr spectrum includes a two-proton singlet at 4.1 ppm corresponding to the resonance of the bridging-CH_2-protons.

This compound was reacted with 1 mol equivalent of MSH to give an oil which was treated directly with acetic anhydride in a queous ethanol to give the diionic species (158) as a straw coloured oil. Alkylation was effected by heating with methyl iodide in refluxing acetone to afford the metho salt (159) as a yellow foam. Treatment with aqueous cyanide before gave the 4-cyanopyridine (132) which was purified by leeching with ether or by column chromatography on basic alumina. From ether the product crystallizes as colourless prisms and in the pmr spectrum (d^6DMSO/$CDCl_3$) shows the bridging -CH_2- protons giving rise to a singlet at 4.3 ppm. The α-pyridine protons resonate as a singlet at 8.8 ppm and a doublet (J=5Hz) at 8.6 ppm. The indole N-H resonance appears as a broad singlet at 10.4 ppm and those due to the remaining aromatic protons as two, three-proton complex signals at 7.1 and 7.4 ppm. The mass spectrum shows a molecular ion peak at m/e 233. In an attempt initially to hydrolyse the cyanide function this compound was heated for two hours in boiling 2N hydrochloric acid giving a red solution which was neutralised with dilute ammonium hydroxide. Extraction with chloroform yielded a pale yellow solid which could not be crystallized. Solutions of this compound fluoresce strongly under ultra-violet light but darken on standing. Ellipticine and many of its derivatives exhibit similar fluorescent



(160)



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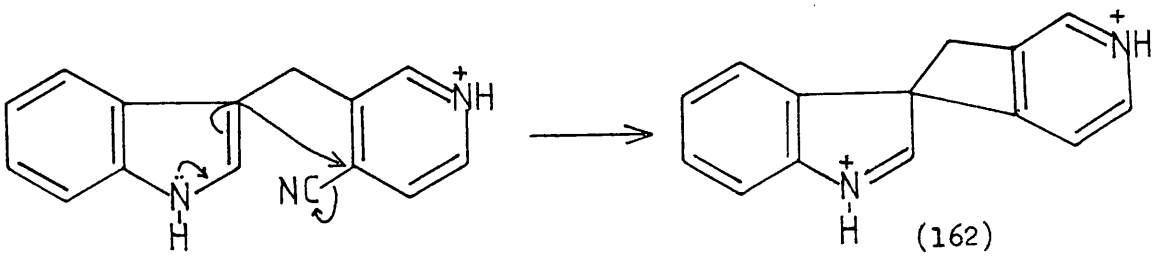
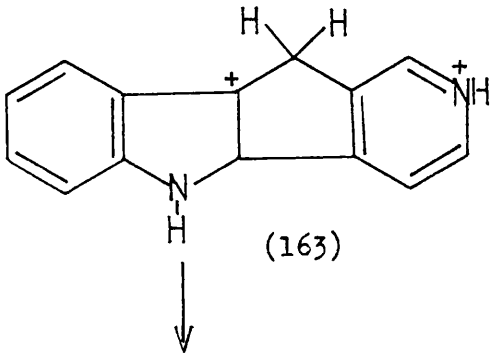


(162)



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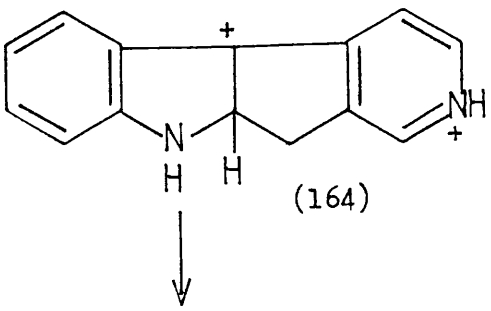


(164)

(160)

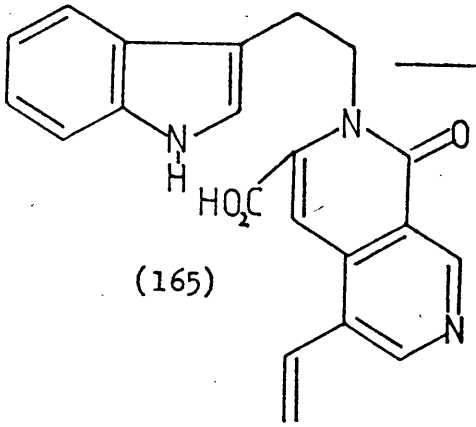
(161)

properties and although we thought it unlikely that hydrolysis and subsequent cyclisation had occurred under the conditions employed it was clear that some reaction had taken place.

The ultra-violet spectrum of the solid obtained from this reaction displays maxima at λ228, 250 and 335 nm with a shoulder at 346 nm. This spectrum is similar to that of 3-nicotinoylindole and we concluded that the unknown compound possessed extended conjugation with respect to the carbonitrile starting material. This suggested the possibility of the formation of a tetracyclic system, the exact nature of which was still to be determined.

The infra-red spectrum shows prominent peaks at 3400 and 1605 cm^{-1}, there is no evidence of a C≡N stretching absorption. The pmr spectrum helped considerably in the elucidation of this structure displaying the familiar two-proton singlet at 3.8 ppm due to the $-CH_2-$ bridging group. The rest of the spectrum consists of an indolic N-H signal at 11.6 ppm, a singlet at 8.8 ppm, a doublet (J=5Hz) at 8.6 ppm and two complex series of signals at 7.7 and 7.3 ppm corresponding to three and two protons respectively. The mass spectrum shows the presence of a molecular ion peak at m/e 206 and since this is two mass units less than the starting picolylindole we concluded that the structure we were dealing with was either the tetracycle (160) or, less likely, its isomer (161).

We favour the first structure since although cyclisation to C-2 of an indole is normally preceeded by attack at C-3 followed by rearrangement in our case the necessary intermediate (162) would contain a highly strained four-membered ring. In the unlikely event of such a reaction one might consider that of the two carbonium species required for subsequent rearrangement (163) is more stable than (164)



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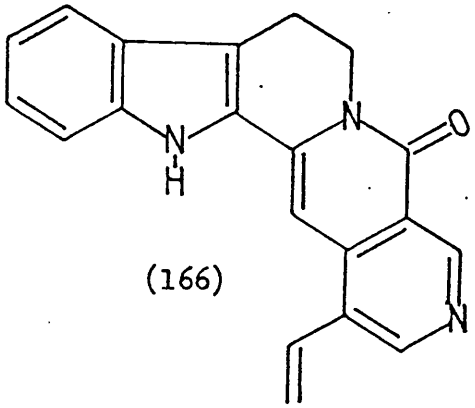

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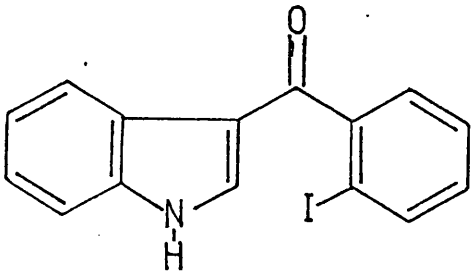

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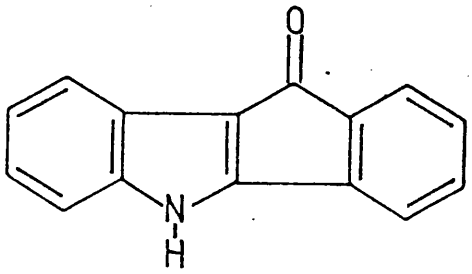

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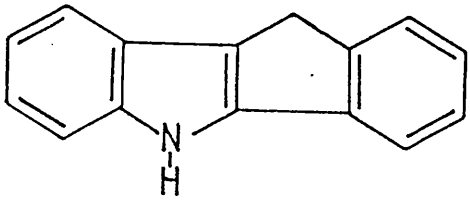
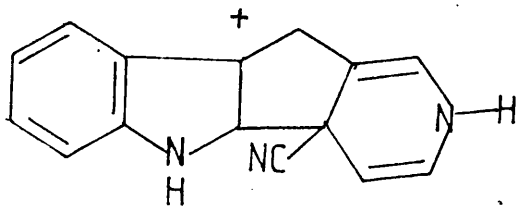


(169)



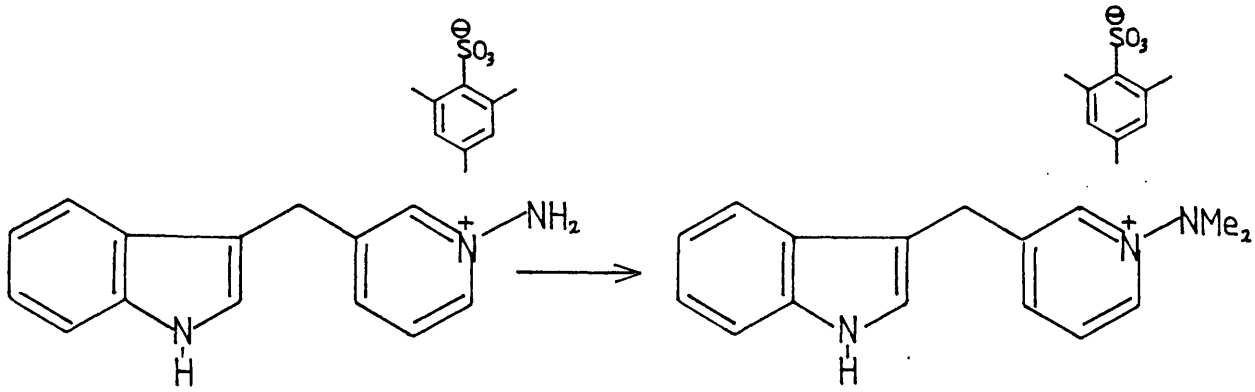
(170)

but under the conditions of the reaction both tend to be de-stabilised. It would seem therefore that attack at C-2 takes place directly to give isomer (160). There is, of course, ample precedent for this type of reaction. Kametani and his co-workers have reported recently[64] that the 7-azoisocarbostyril (165) forms angustine (166) when heated with a mixture of acetic and hydrochloric acids.

Interestingly photolysis of 3-o-iodobenzylindole (167) gives indeno (1,2-b)indol-10(5H)-one (168)[65] which has been reduced with lithium aluminium hydride to give 5,10-dihydroindeno(1,2-b)indole (169). The ultra-violet spectrum of this last compound almost identical with that of our product.

It is unclear whether the formation of (160) is preceeded by hydrolysis of the nitrile function to a carboxylate group prior to ring-closure or whether a dihydropyridine of the type (170) is involved as an intermediate. Under the conditions we employed the latter case seems much more plausible.

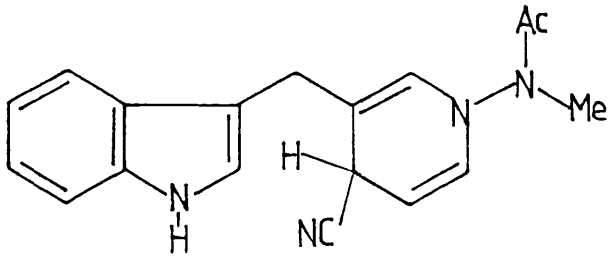
In order to provide further evidence for the structure of (160) we attempted to acetylate the indole N-atom. This acetyl derivative could then be used in pmr studies designed to establish the deshielding influence of the carbonyl group on adjacent protons and differentiate between (160) and (161). For example the carbonyl group would have a considerable effect on the chemical shift of the methylene bridge proton resonance in structure (161) whereas in (160) much less change would be anticipated. Unfortunately such a derivative was not obtained in the pure state, - a result which is difficult to rationalize. Treatment with acetic anhydride under various conditions gave green solutions which when worked-up yielded dark products. We were unable to effect a satisfactory purification but the pmr spectra of these crude products included singlet absorptions at δ 3.7 and 1.85 ppm, a feature which tends to support structure (160).



(171) (172)

Table 5

Chemical shift		Multiplicity	Number of protons
$CDCl_3$ at 60MHz	d^6DMSO at 100MHz		
8.6	10.9	bs, (exchanges with D_2O)	1
7.7-7.0	7.6-6.8	complex	5
6.1	6.4	m	1
5.9	6.35	bs	1
4.7	4.65	m	1
4.1	4.1	bd	1
3.6	3.6	two lines	2
3.1	2.95	two lines	3
2.1	1.95	two lines	3



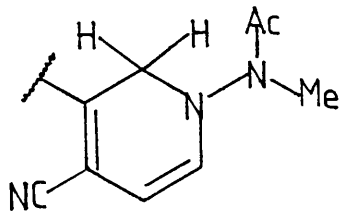
(173)

A ^{13}C nmr spectrum was recorded which confirms either structure (160) or (161) but does not clearly differentiate between them. Further work in this laboratory is designed to establish the correct structure once a derivative containing a heavy atom can be prepared in suitable crystalline form.

We decided to prepare a sufficient quantity of this new compound for an initial biological evaluation and we therefore had to synthesise additional amounts of the 4-cyanopyridine (132). A larger scale preparation from 3-picolylindole appeared to proceed smoothly until reaction with methyl iodide gave yellow prisms rather than the usual more amorphous material. The pmr spectrum of the product showed the presence of a mesitylene unit with two additional three-proton singlets. From this information we realised that the reaction of the salt (171) with acetic anhydride had failed and that subsequent methylation yielded the compound (172). This material proved unreactive under the conditions employed for the cyanide addition reaction.

Another diversion occurred soon after this minor set-back when a white solid was isolated from the reaction with cyanide ion prior to ultra-violet irradiation. In the pmr spectrum this material displays the signals shown in Table 5.

It was apparent that we were dealing with a dihydropyridine system once again. It is probable that the complexity of the signals is increased by conformation isomerism (rotomers) but when elevated temperature spectrums are recorded a progressive change to the spectrum of the fully aromatic nitrile (132) is noted. This transformation is rapid at 120° but at intermediate temperatures a gradual coalescence of the signals at 1.9, 2.9 and 3.6 ppm into singlets is observed and as the temperature is raised signals arising from N-methylacetamide begin to appear. These latter signals increase in intensity as those due to the pyridine N-substituent diminish and this data can best be interpreted in terms of the dihydropyridine (173). It seems less likely that the two



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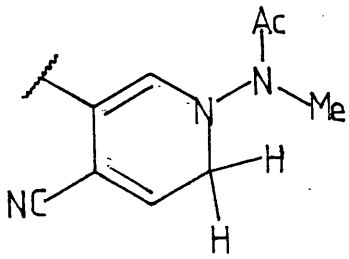

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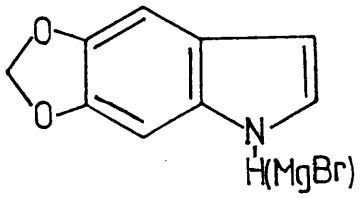

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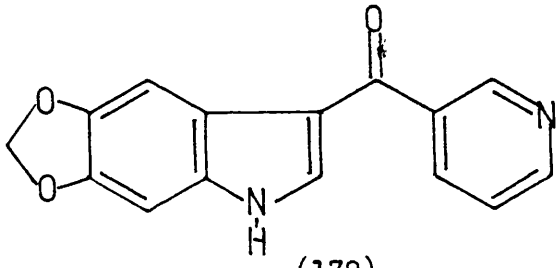

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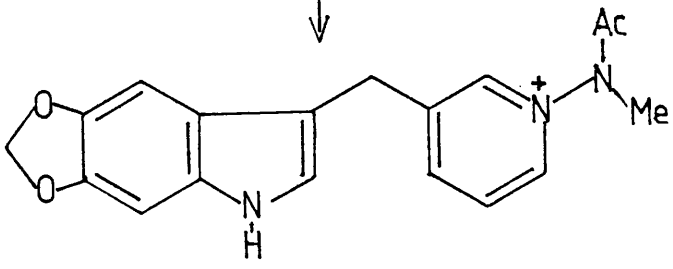

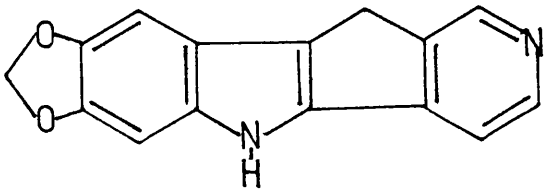

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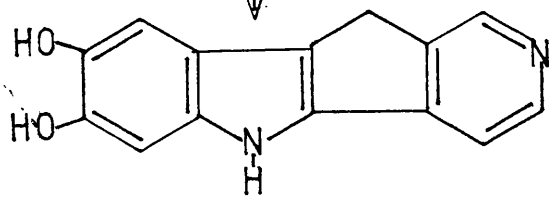


(178)

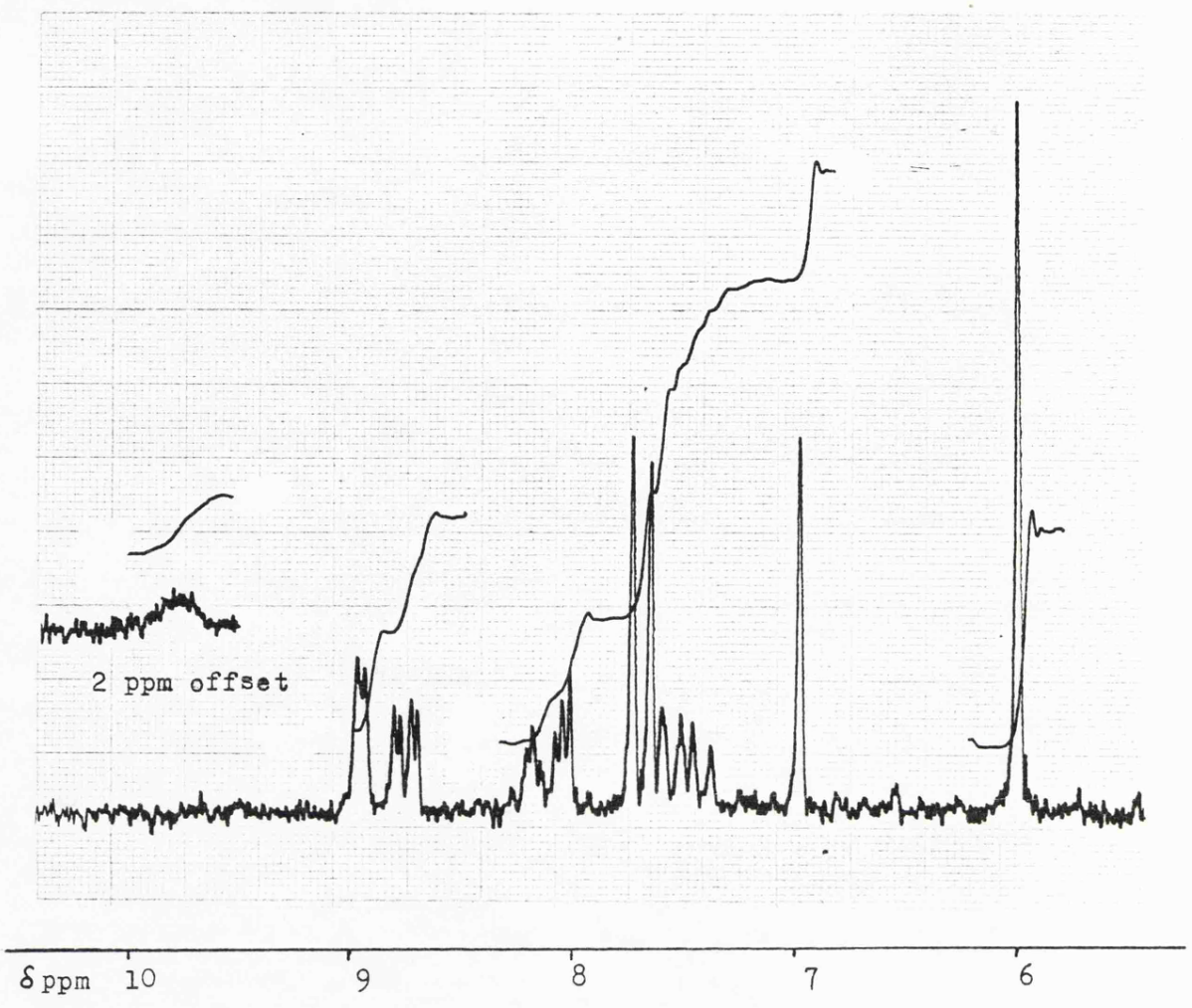
alternatives (174) or (175) are present since nowhere within the spectrum are there coupling constants of the order of 15Hz expected for the spin-spin interaction of geminal methylene protons present in these structures.

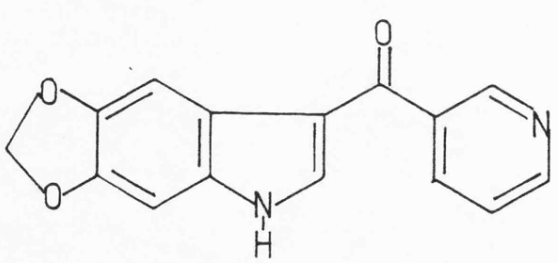
The single proton, broadened doublet ($\underline{J}$=5Hz) at 4.1 ppm may be assigned to the signal of H-4 coupled strongly to H-5 and weakly affected by H-2 and H-6. The H-5 signal occurs at 4.7 ppm as a six line pattern which is simplified when the signal at 4.1 ppm is subjected to a second radiofrequency. The broadened, one-proton singlet at 5.9 ppm is the resonance of H-2 while that of H-6 gives rise to a multiplet at 6.1 ppm. The pair of two line systems at 2.1 and 3.1 ppm correlate with the resonances of the N-acetyl and N-methyl protons of the pyridine nitrogen substituent. The methylene-bridge protons appear as a singlet at 3.6 ppm and the indole N-H as a broad singlet at 8.6 ppm. Finally the indole protons absorb as a complex set of signals between 7.0 and 7.7 ppm.

To determine the rate of aromatisation at room temperature a sample in an nmr tube was left to stand and spectra taken after varying periods of time. Thus after 48 hours the sample was 36% 'aromatic' and was a 50:50 mixture after 3 days. It was only after 10 weeks had elapsed that no trace of the dihydrocompound could be seen.

We eventually obtained enough of the 4-cyanopyridine to enable us to prepare a sample of 10$\underline{H}$-Indolo(3,2b)-2-azaindene (160) sufficient for an initial biological evaluation. Having rather stumbled across this interesting system we sought to prepare a derivative possessing a methylenedioxy group (176) since we had access to a limited quantity of methylenedioxyindole (177). Thus we envisaged a series of reactions giving rise to (176) or possibly the dihydroxy derivative (178).

The pyrido-indole (179) was obtained, albeit in low yield, as a white solid from the reaction of the Grignard reagent and nicotinoyl

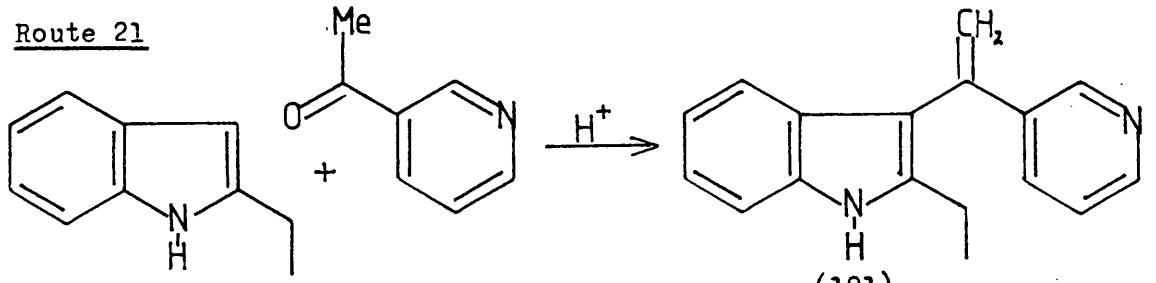

2 ppm offset
δ ppm
10
9
8
7
6


O
O
O
N
N
H

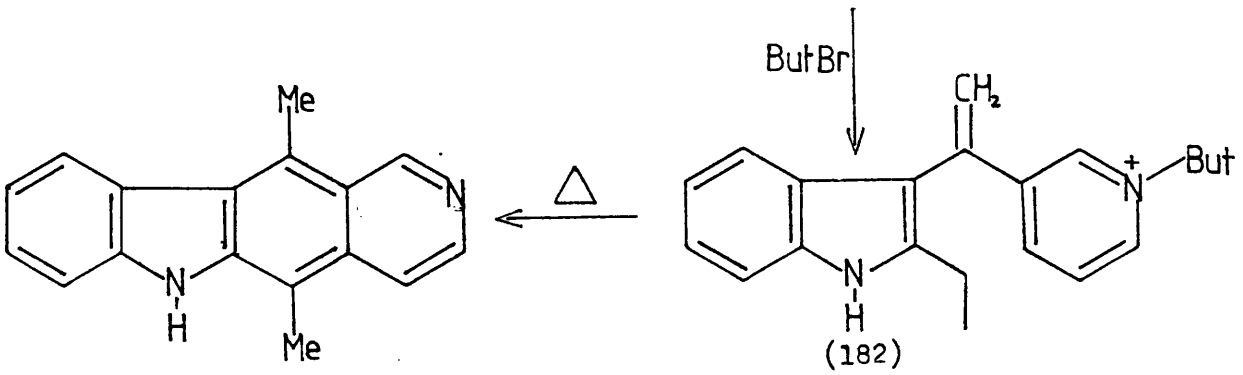
chloride. The infra-red spectrum displays absorptions at 3200 and 1600 cm^{-1} while the pmr spectrum includes a two-proton singlet at 6.0 ppm due to the resonance of the methylene protons. The indole 2-proton absorbs as a broadened singlet at 7.6 ppm which is sharpened on the addition of deuterium oxide. The indole 4-and7- protons give rise to singlet resonances at 7.7 and 7.0 ppm respectively.

When this material was treated with sodium borohydride in boiling ethanol we recovered a small amount of a brown oil which was subjected to the usual sequence of reactions to give, after alkylation with methyl iodide, a dark gum. From TLC and pmr data it was apparent that we were dealing with a complex mixture and we decided to postpone further work in this area since the time required to synthesise additional quantities of methylenedioxyindole would have been prohibitive.

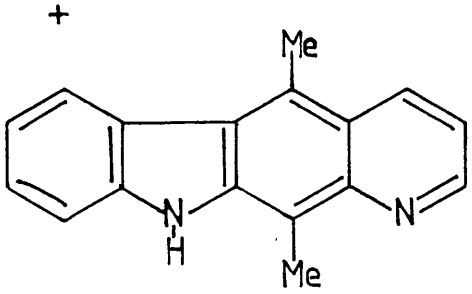
Route 21



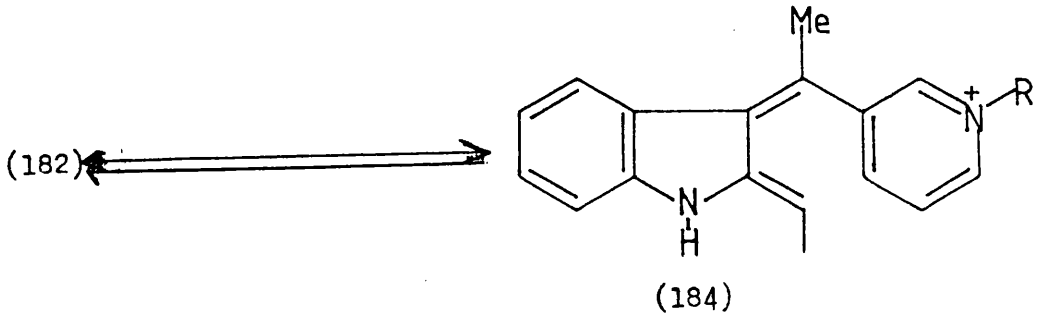
(180) (181)



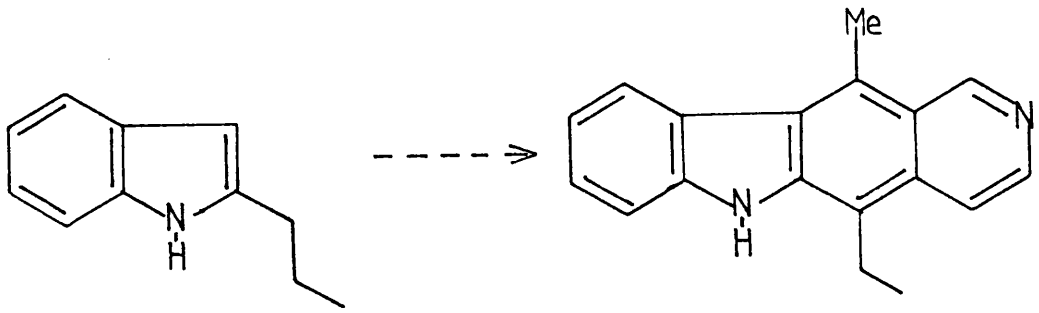
(182)



(183)



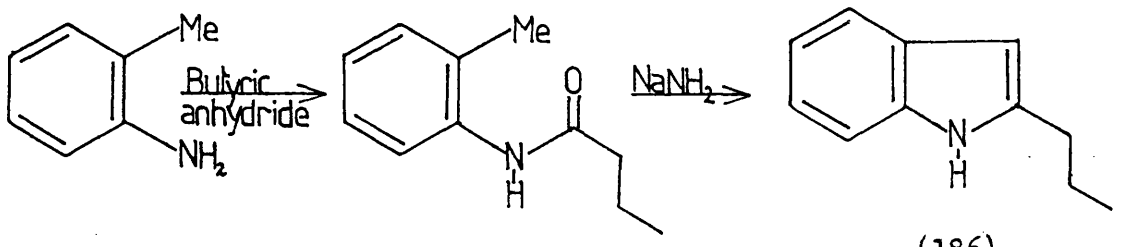
(182) (184)



(186) (189)

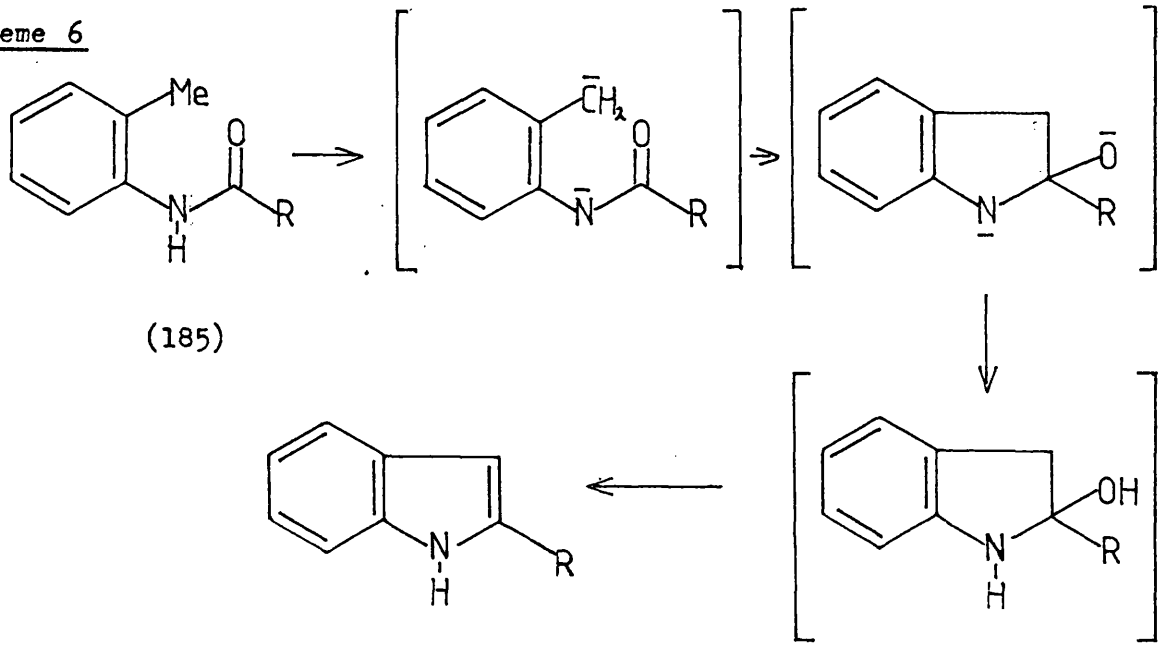
The Investigation of a new Synthesis of Ellipticine

It was at this time that we learned of a new, simple synthesis[66,67] of the alkaloid developed by Dr. Jan Bergman of the Royal Institute of Technology in Sweden. He has previously shown[68] that 2-ethylindole (180) can be effectively condensed with 3-acetylpyridine under strongly acidic conditions to give 1-(2-ethyl-3-indolyl)-1-(3-pyridyl) ethene (181), ie a '1,1 product'. The formation of a '2,1 product' is inhibited by the bulky substituent in the indole 2-position. In the new synthesis compound (181) is quaternised with butyl bromide and the resulting pyridinium salt (182) is pyrolysed at a temperature above 350° for a short period to give ellipticine in 72% yield (Route 21). The introduction of the N-butyl group activates the pyridine ring to nucleophilic attack and this may lead to reaction by the enamine system in the exocyclic tautomer (184) of (182). Since both the α- and γ-sites in the pyridinium ring are activated the appearance of the isomer (183) in reaction mixtures is not surprising but it was found that the rate of heating during the pyrolysis was critical for optimum yields of ellipticine. A slow rate of heating gives predominantly (183) whereas rapid heating of the salt (182) gives a good yield of the alkaloid itself. These features of the reaction have not been adequately explained and the appeal of the synthesis is somewhat limited because of the harsh pyrolysis step. This is especially important since many ellipticine derivatives are thermally unstable. The excellent yields reported by the Swedes prompted us, despite these limitations, to investigate the scope of the synthesis by attempting to prepare 5-ethylellipticine (189) from the propyl indole (186). As well as preparing a new derivative the exercise promised to provide an interesting comparison with our own synthetic

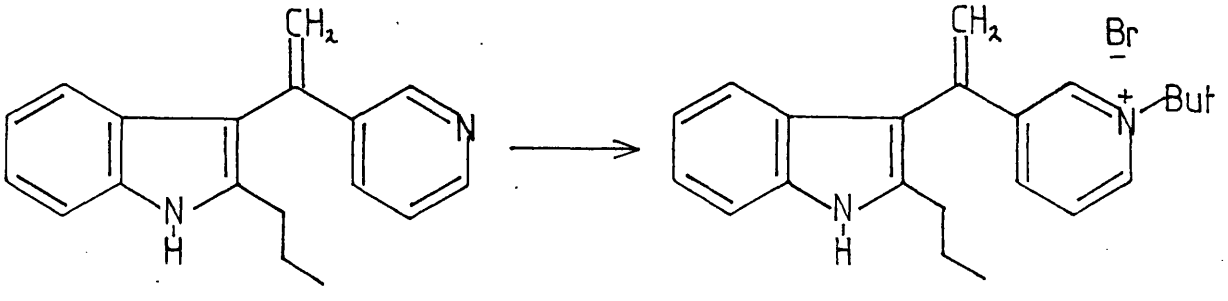


(185) (186)

Scheme 6



(185)



(187) (188)

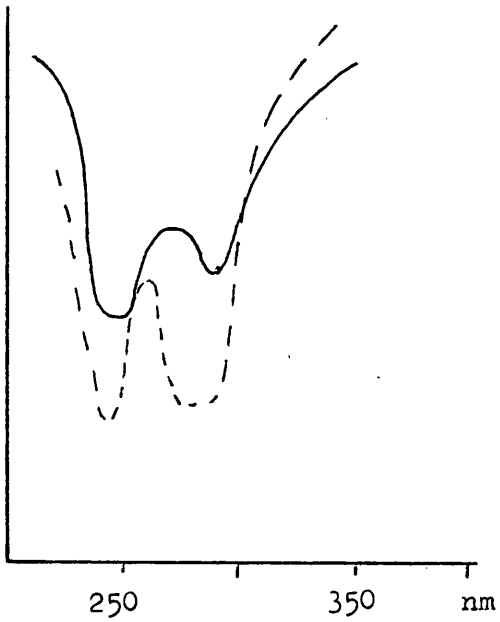
route[28] to 5-alkylellipticines. 2-Propylindole (186) was prepared from the N-substituted-o-toluidine(185) via a Madelung reaction[69]. It is generally accepted[70] that this reaction proceeds via a dianion intermediate which cyclises and yields the indole after loss of water. (Scheme 6). Thus theoretically two moles of sodamide are used but in practice we used a three molar excess to obviate any problems arising from the presence of acidic impurities in the toluidine.

Reaction of 2-propylindole with 3-acetylpyridine in refluxing methanolic hydrogen bromide furnished (187) in good yield as colourless prisms. The pmr spectrum of this compound displays the propyl group resonances as a three proton triplet at 0.85 ppm, a two proton multiplet at 1.6 ppm and a two proton triplet at 2.6 ppm. The ethylenic protons absorb as a pair of finely split doublets at 5.4 and 5.8 ppm while a five proton multiplet centred at 7.1 ppm corresponds to the indole protons plus the β-pyridine proton. The indole N-H absorption appears at 8.9 ppm and the α-pyridine protons give rise to signals at at 8.8 and 8.4 ppm. Finally a pair of finely split triplets at 7.6 ppm correspond to the γ-pyridine hydrogen atom.

This compound was heated with n-butyl bromide in a range of solvents without reaction but when neat alkyl halide was employed a dark gum was deposited after several hours of heating. Decantation of the excess butyl bromide yielded, on cooling, a brown glass. The pmr spectrum of this material, (188), shows the presence of the C_4H_9 unit while the α-pyridine protons are strongly deshielded, absorbing below 9 ppm.

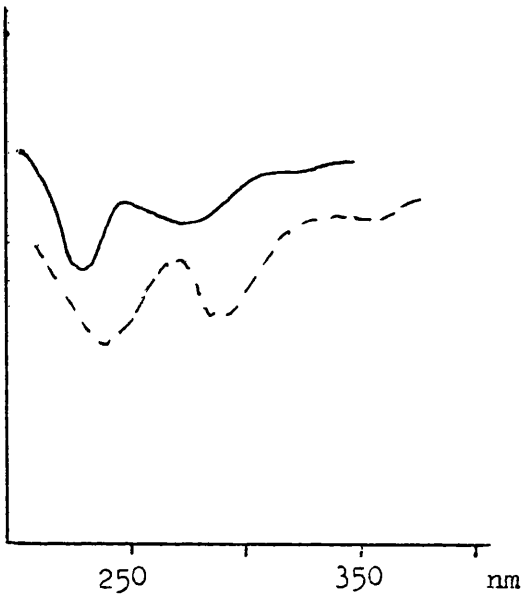
Preliminary experiments involving the heating of small amounts of the powdered salt (188) in a melting-point apparatus and subsequent ultra-violet spectral analysis suggested, as reported by the Swedish workers, that rapid heating to temperatures in excess of 350° gave optimum results (the absorption spectrum of 6-H-pyrido(4,3-b) carbazole

Ultra-violet spectra of samples from pyrolysis experiment



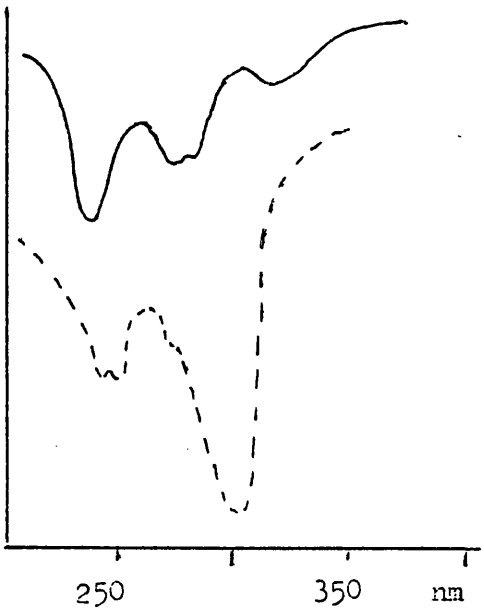
——— (187)

- - - - (188)



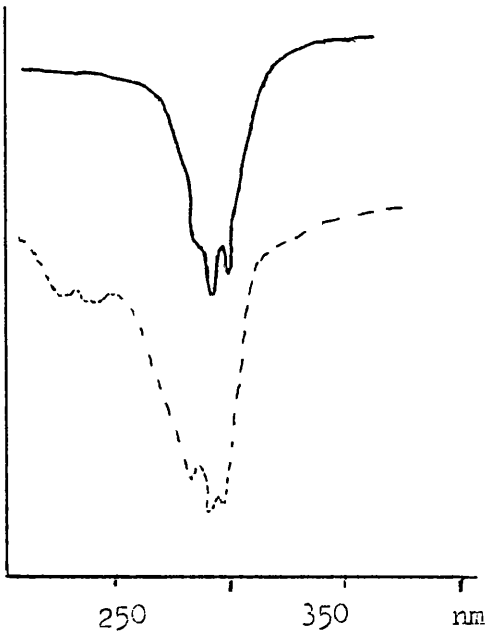
——— (188) heated slowly 80-250°

- - - - 190-300°



——— rapid heating to 350°

- - - - crude product from column

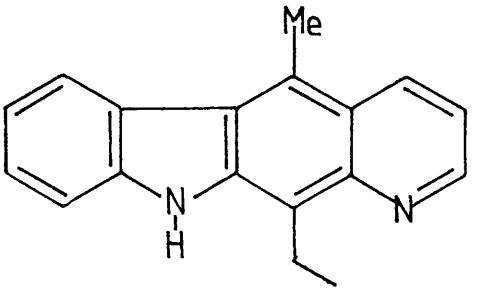


——— 5-ethylellipticine

- - - - ellipticine

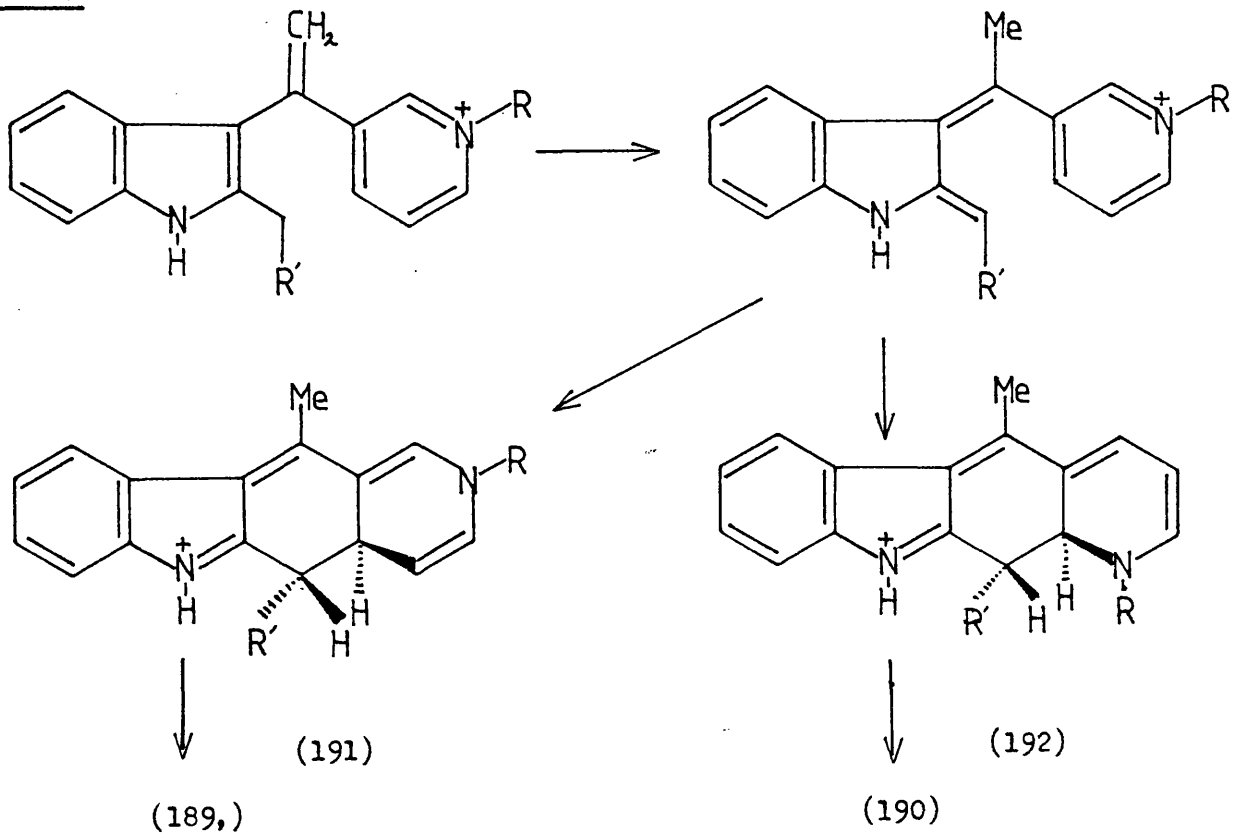
is characteristic).

Initial pyrolysis experiments using pre-heated oil- and metal-baths proved disappointing with TLC and spectral data suggesting the presence of only small amounts of aromatic tetracyclic product. It was found difficult to maintain temperatures much in excess of 350° and prolonged periods of heating led to the recovery of substantial amounts of charred material. We next tried a reaction employing a high boiling silicon oil but again unsatisfactory results were obtained. Finally, however, when the salt was simply heated over a luminous Bunsen flame for several minutes we obtained a dark coloured product which, by TLC analysis was shown to consist of several highly fluorescent components. The crude material was chromatographed on silica and elution with diethyl ether yielded a small amount of a fluorescent, blue gum which we were unable to characterise. Elution with ether/chloroform mixtures yielded a yellow solid which was purified by vacuum sublimation followed by several recrystallisations from ethanol to give a small quantity of yellow needles. The mass spectrum of this product shows a molecular ion peak at m/e 260 and, additionally, a facile loss of 15 mass units, consistent with the molecular formula of 5-ethylellipticine and the loss of a methyl unit (from the 11-position). The presence of a peak at m/e 130 is also consistent with the proposed structure since a half-molecular ion peak is characteristic of many ellipticine derivatives. The pmr spectrum in d^6DMSO shows the presence of the ethyl group as a three proton triplet at 1.3 ppm and a two proton quartet at 3.4 ppm. The signal due to the resonance of the 11-position methyl group appears as a singlet superimposed on the quartet at 3.35 ppm. The indole N-H signal appears at 12.2 ppm while two, three proton complexes at 7.3 and 8.3 ppm correspond to the aromatic hydrogens. H-1 absorbs as a low-field, slightly broadened singlet at 9.9 ppm. The ultra-violet



(190)

Scheme 7



(189,)

(191)

(192)

(190)

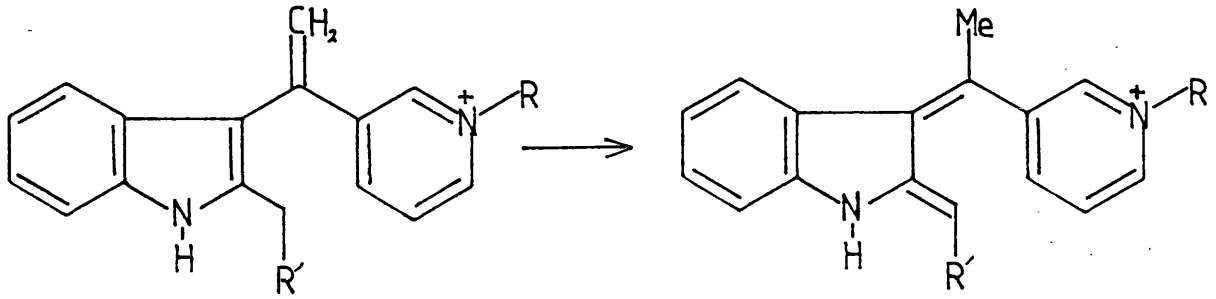
and infra-red spectra, as might be expected, are very similar to those of the parent alkaloid.

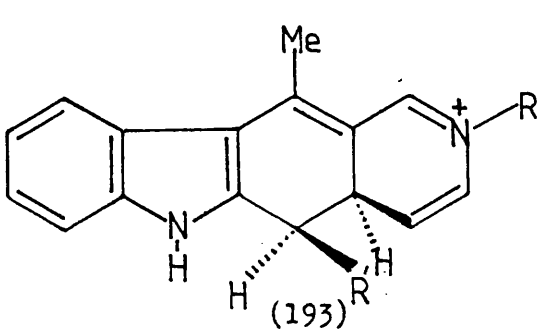
Our satisfaction at having isolated this derivative was tempered by the extremely poor yield - of the order of 1%. Later fractions obtained from the column eluting with solvents of increasing polarity were shown, by TLC, to contain additional amounts of 5-ethylellipticine but we were unable to obtain further quantities of pure material. It must be stressed however that we did not expend any additional time in optimizing the conditions and it is likely that differing techniques are required for the pyrolysis of varying substrates.

Interestingly, we did not observe any of the alternative isomer (190), which from the experiences of the Swedish chemists should predominate in 'low' temperature experiments. However, the mechanism of the cyclisation reaction is far from clear. Bergman and Carlsson[71] suggest that at temperatures below or close to 350^0 an ionic mechanism (Scheme 7) operates. They conclude that α-substitution of the pyridinium nucleus is favoured under these conditions. The literature abounds with examples [72] where both α-and γ- nucleophilic attack to pyridinium salts occur, but apart from a preliminary discussion by Kosower[73] in which he stresses the role of charge-transfer complexes en route to the γ-products, a strict rationale indicating which process is preferred is still missing. Indeed, we have already noted (page 33) how a minor change in solvent conditions may apparently alter the isomer ratio. Since, however, the salts (eg.188) are simply heated solvent effects cannot apply in this case.

To account for the change in product ratio as the temperature is raised the Swedes propose that a concerted reaction now comes into effect (Scheme 8). They argue that the conformation (193) is more populated than (194) so that the cyclisation is directed in favour of ellipticine. It is clear that of these two products (194) is more

Scheme 8

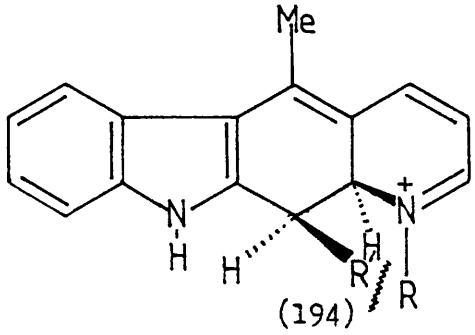




(193)

1. $-H_2$
2. -But Br

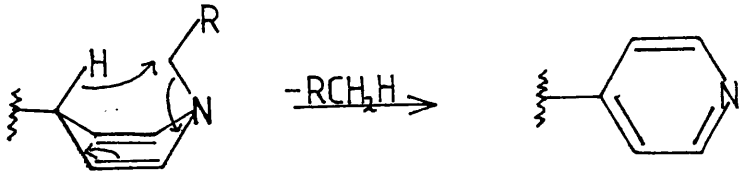
(189)



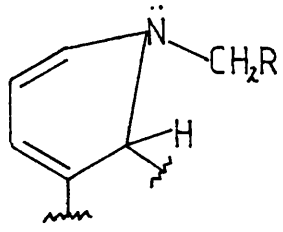
(194)

1. $-H_2$
2. -But Br

(190)



(191a)



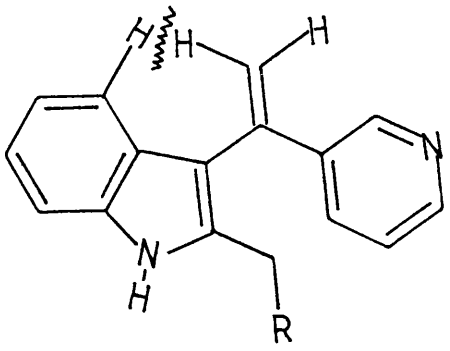
(195)

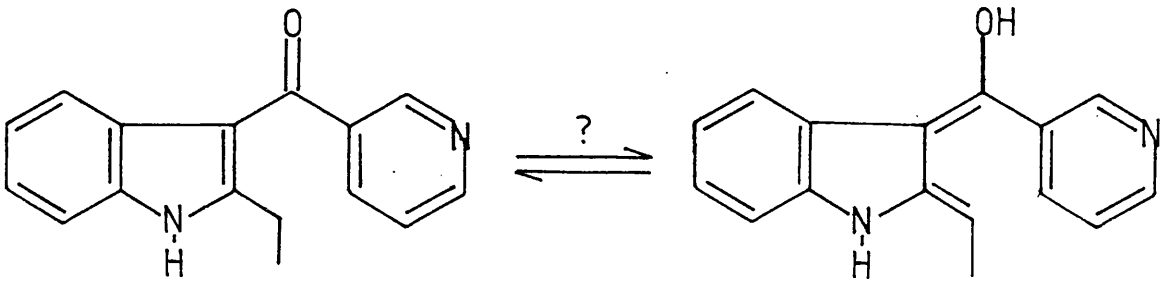
sterically constrained and this would certainly exert a strong effect on the path of the reaction.

If the reaction proceeds *via* only one mechanism it is unlikely that it is a concerted sequence for at low temperatures the sterically hindered intermediate (194) is clearly disfavoured. The ionic reaction path could, however, account for the changing product ratios because, unlike the orbital symmetry controlled concerted process the required intermediates may adopt the most economical geometries, (191) and (192), and then the thermally induced changes simply reflect a delicate balance between thermodynamic and kinetic control factors. However, the concerted process does not require alkylation of the pyridine nitrogen atom whereas the ionic mechanism depends upon this factor. When the parent pyridine, rather than the salt, is heated cyclisation still occurs but the efficiency is very much reduced and equal amounts of ellipticine and isoellipticine are formed.

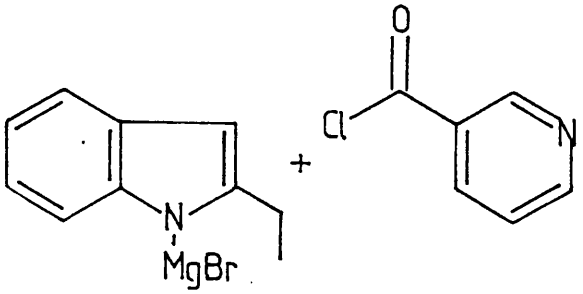
The requirement of an N-n-butyl substituent is one further curious feature of this ellipticine synthesis. Bergman and Carlsson record that the proportion of ellipticine relative to isoellipticine obtained drops from 13:1 to less than 2:1 if other primary (or secondary) alkyl units are present, and that butane and butyl iodide are formed during the reaction. Presumably butane arises through an intramolecular process, for which the intermediate (191), in the boat conformation, would be an ideal substrate (see page 35). The alternative dihydropyridine (195) (c.f. page 35) is much less suited to this dealkylation step and might be expected to aromatise in a sequential manner. Even so, the formation of butyl iodide is not easily explained - unless de N-alkylation is the first step.

Both the ionic and the concerted schemes require a (1,5) prototropic shift to form the presumed intermediate (184). Such shifts

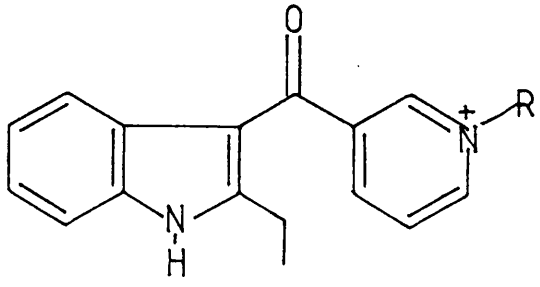




(196) (197)



(196)



(198, R=n-But)

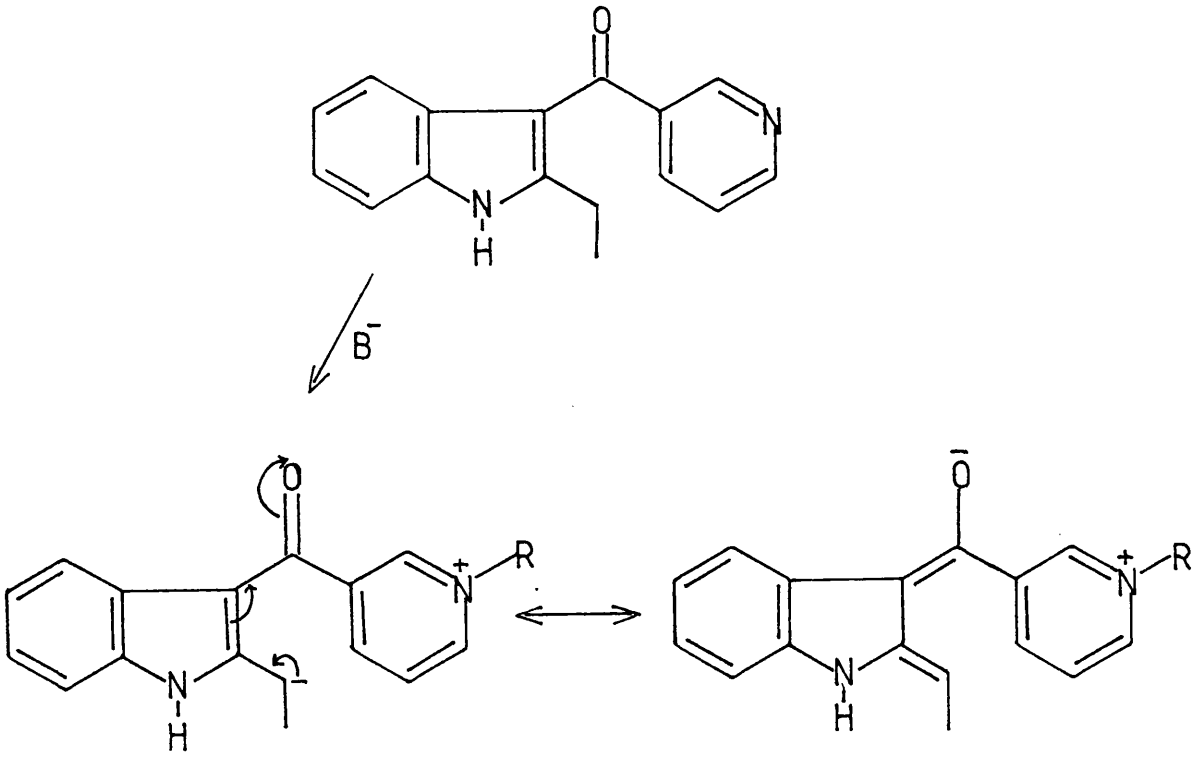
(199, R= $-N(Me)COCH_3$)

may occur in a step-wise manner, although a concerted symmetry allowed suprafacial change is also commonplace. In this case the shift is facilitated by the relief of steric interaction between the methylenic proton and the C4-H indolic hydrogen. The free rotation of the methyl group in (184) allows the molecule to adopt a more favourable geometry.

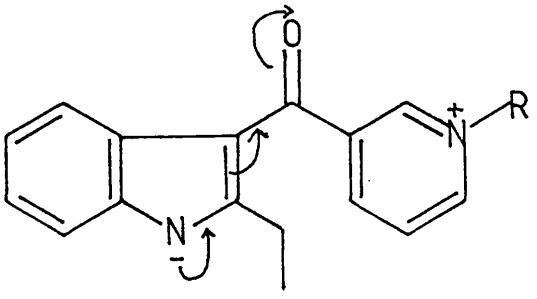
It is clear that this synthesis raises so many questions of mechanistic detail that much work remains to be done upon it and it is also certain that considerable experience is required to obtain good results from pyrolysis experiments as shown by our poor yields as compared to those obtained in Stockholm.

We decided at this point that it would be profitable if we diverted our attention to the ketone (196). The methylene protons of the indole α-substituent should be rather more acidic than those of the salts (i.e. 188) so that the presence of the tautomeric form (197) might be observed. By altering the pH of the reaction medium a change in the position of the equilibrium in favour of the enol (197) might be effected. Even if (197) were only a minor component we felt that thermolysis and possibly photochemical reactions, hopefully leading to tetracyclic products, warranted investigation. Thus the ketone (196), prepared by the reaction of 2-ethylindolylmagnesium bromide with nicotinoyl chloride, was obtained and, interestingly, in several coloured forms. Pmr studies showed that these samples were identical and it was noted that a purple solution in DMSO turned yellow on the addition of chloroform. The spectrum of this compound displays the ethyl group resonances as a three proton triplet and a two proton quartet at 1.3 and 2.9 ppm respectively. The α-pyridine protons resonate as a finely split ($\underline{J}$= $1H_z$) doublet at 8.9 ppm and a pair of doublets ($\underline{J}$=$1H_z$ and $\underline{J}$=$5H_z$) while the remaining aromatic protons absorb between 6.9 and 7.6 ppm.

The quaternary salt (198) was prepared, as before, by heating



(200)

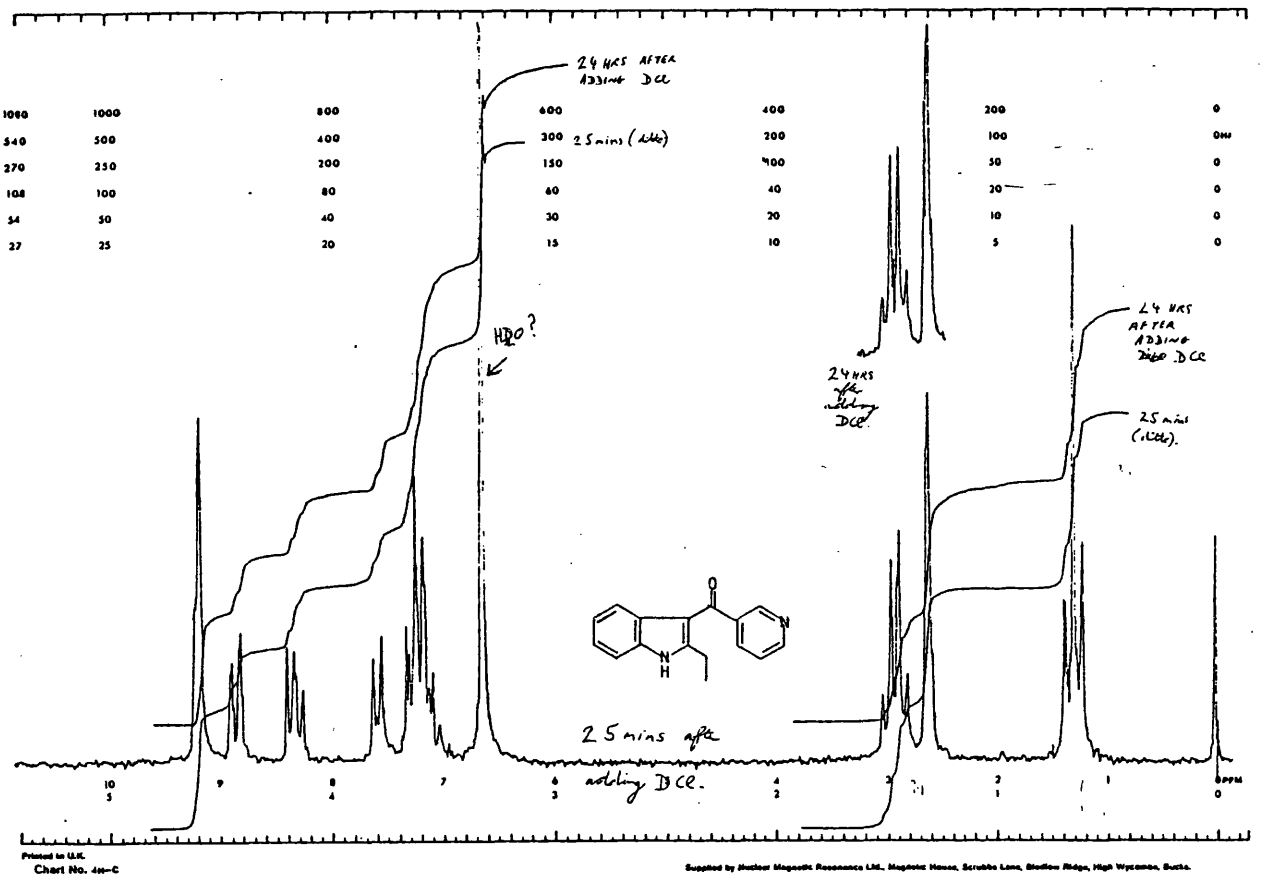


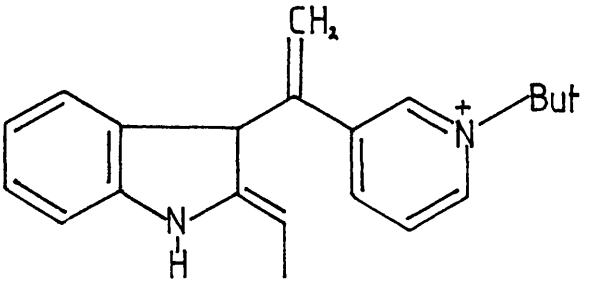
the ketone with butyl bromide. To initiate proceedings both the salt and the ketone were subjected to pyrolysis over a Bunsen flame and in both cases a dark, crispy mass was obtained. TLC analysis showed that both samples were complex mixtures and in particular it was noted that the product from the pyrolysis of the salt contained several highly fluorescent components. This hint of success prompted strenuous efforts to effect a satisfactory separation. However, chromatography, gel filtration and sublimation gave mainly dark, intractible material and we were unable to determine the nature of the fluorescent components.

When either of the above substrates were pyrolysed using lower temperatures charring was reduced but no useful products were obtained. TLC analysis suggested the presence of substantial amounts of starting material.

We next investigated the use of a more labile quaternising function since we suspected that the high temperatures were, at part at least, required to cause ejection of this group. The aminated compound (199) was therefore prepared and subjected to thermolysis over a range of temperatures but once again we were left with intractible mixtures.

At this point we diverted our attention slightly to the generation of the carbanion (200) by treating the salt (198) with base. We did not anticipate total conversion to this anion because of the presence of the more acidic N-H group but we reasoned that if only a small amount was generated subsequent cyclisation should proceed easily and shift the equilibrium in favour of a tetracylic product. Since the 2-methyl group of 2,3-dimethylindole is completely deuteriated under mild acidic conditions [74] and examples [75,76] of tautomerism of 2-alkylindoles followed by electrophilic attack have been recorded

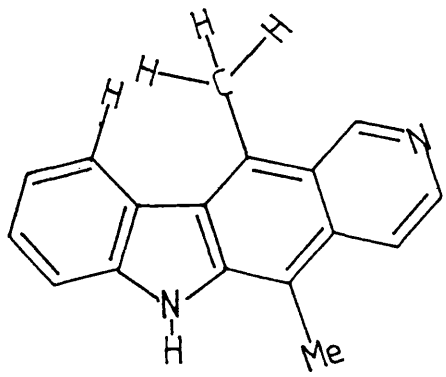

24 HRS AFTER ADDING DCl
25 mins (CH2Cl2)
HDO?
24 HRS after adding DCl
25 mins (CH2Cl2).
25 mins after adding DCl.
PPM


CH2
But
N
H

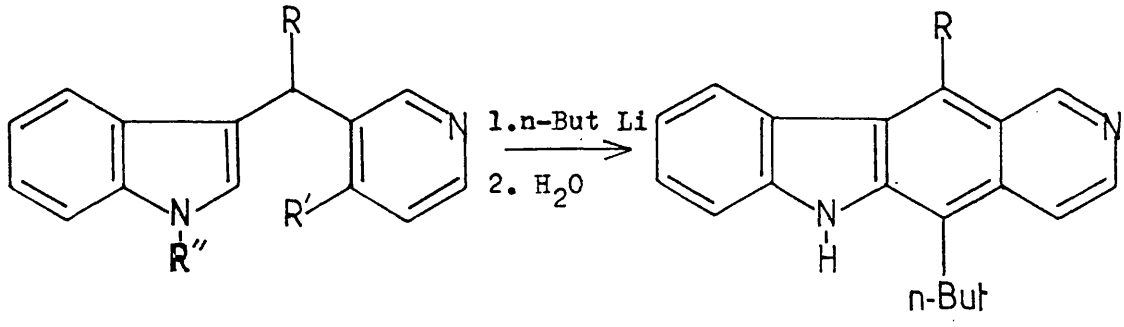
we felt that we should have a good chance of success. However, treatment of the salt (198) with sodium ethoxide returned only starting material under a variety of conditions. This caused us to question the acidity of the methylene protons and we next treated the ketone (196) with deuterium oxide for several days. No exchange was observed, either in this experiment or when deuterium chloride and deuterium oxide were used. It is evident that the N-H group is sufficiently more acidic than the methylene protons to effectively suppress formation of any of the desired carbanion. Predictably, when the indole N-acetyl derivative was treated with base only de-N-acetylated starting material was obtained.

In a final attempt to effect a satisfactory cyclisation of this type of compound we employed photochemical methods on both (187), (196) and the respective N-butyl pyridinium salts (189) and (198). All these attempts failed, returning only unchanged starting material, presumably because of the difficulty in generating the necessary trienic system. A (1,5) suprafacial hydrogen shift is disallowed photochemically and an allowed (1,5) antarafacial shift would involve a highly strained intermediate and is not likely. Similarly, two (1,3) hydrogen shifts seem improbable while the product arising from one such shift (201) is unsuitable for eletrocyclic ring-closure.

Since any chance of success using a combination of the above methods also seemed unlikely we abandoned further work in this area in favour of an approach to 5-alkylpyrido (4,3-b)carbazoles based on the Sainsbury and Schinazi route.



Route 22



(82, R=Me, R'=CN, R"=H)

(132, R=H, R'=CN, R"=H)

(205, R=Me, R'=C(But)NH, R"=H)

(206, R=H, R'=C(But)NH, R"=H)

(202, R=Me)

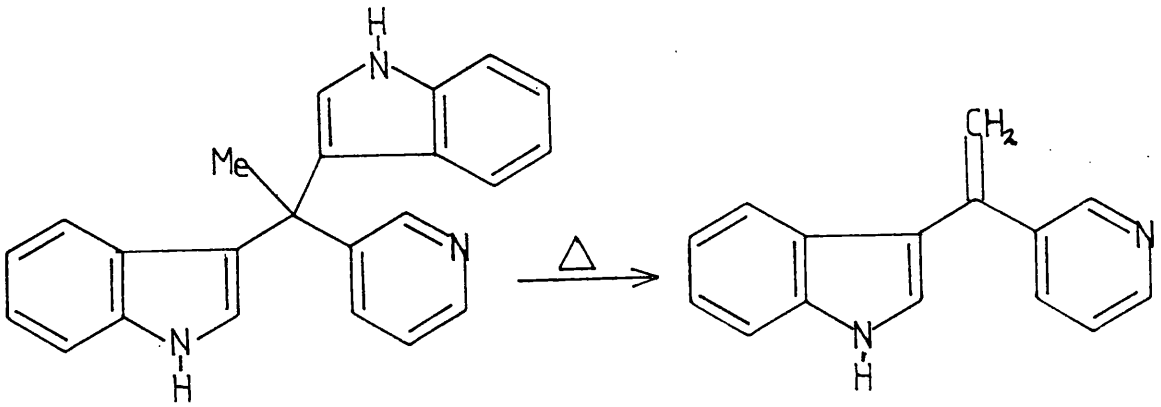
(203, R=H)

The Synthesis of Alkyl Derivatives of Ellipticine

The removal of the methyl group from the 11-position of ellipticine is said[13] to cause a lowering of the pK_A value of 3 units and 11-demethylellipticine has proved to be devoid of anti-cancer activity. Whether this loss of activity is due to the drop in pK_A, which might influence the electronic interaction with DNA or prevents the modified substrate filling some stereospecific site is unknown. It is feasible that the loss of the 11-methyl group allows the pyridocarbazole nucleus to become completely planar since steric-interaction between the methyl group and the C-10 hydrogen atom is now eliminated. However, the loss of therapeutic action could be due to modifications in the permiability characteristics of the molecule which prevents incorporation into the cell. It could be that the methyl groups in the 5- and 11-positions facilitate cell membrane permeation by increasing the lipophilicity of the molecule.

To date, no work has been reported on the effects of larger alkyl groups in these positions despite their probable biological importance and we felt that an investigation was warranted, especially since the route developed in this laboratory[28] lends itself so well to the preparation of this type of derivative.

Synthetically speaking, the preparation of 5-alkyl derivatives presents little challenge since the reaction of lithium alkyls with the corresponding nitriles (Route 22) is fairly certain. However, we also contemplated the synthesis of other derivatives if our preliminary studies proved successful. To initiate proceedings we decided to employ a medium length alkyl chain and we envisaged the preparation of 5-butyl-, and 5-butyl-11-demethylellipticine, (202) and (203), from the reaction of n-butyl lithium and the known nitriles (82) and (132).



(20)

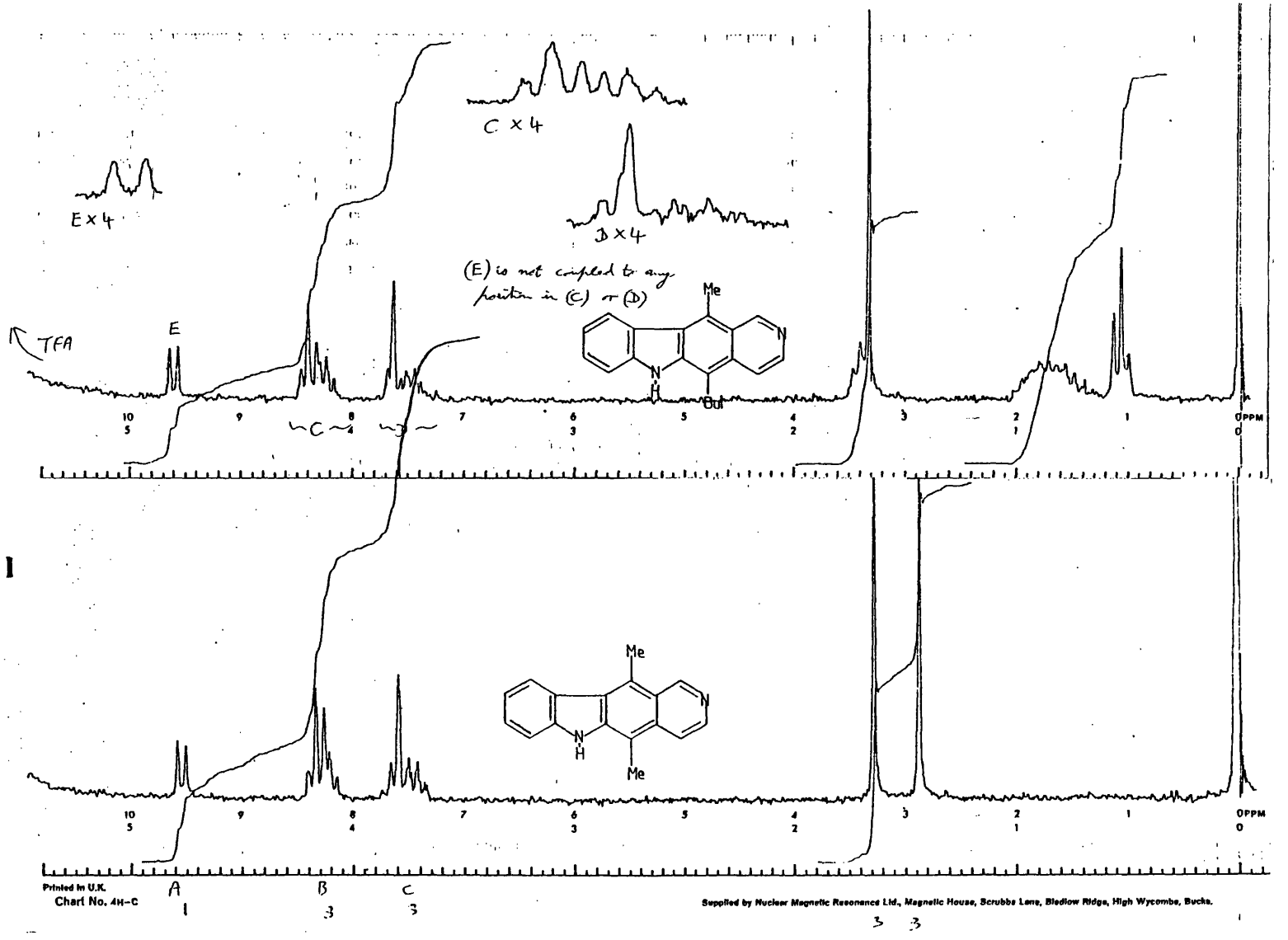
(204)

Pd/C

(79)

The use of (82) required the preparation of the elusive 3-indolylpyridine (79) but fortunately an alternative preparation of this material came to our notice.[69] It was prepared by catalytic reduction of the vinylindole (204) which was, in turn, obtained from the thermolytic cleavage of the bisindolyl derivative (20). This '2,1 product' (see Page 9) is readily obtained from the condensation of indole with 3-acetylpyridine in acetic acid or methanolic hydrogen bromide. Thermolysis of this material at 220°C in vacuo gives the vinyl derivative in a reported 86% yield although in our hands the yield, after chromatography, was not so good. Reduction proceeded smoothly and from the product (79) the nitrile (82,R″=Ac) was obtained as a crystalline solid (Ac_2O-Et_3N : MSH : Ac_2O : MeI : KCN), which in the infra-red spectrum displays a sharp peak at 2220 cm^{-1} and a carbonyl absorption at 1710 cm^{-1}. The pmr spectrum shows the N-acetyl methyl group protons resonating as a singlet at δ 2.7 ppm while the signals at lowest field correspond to the α-pyridine protons and the indole C-7 proton. Indole N-deacetylation may be effected by passage of (82,R″=Ac) down a short column of basic alumina, but in practice we found that treatment with butyl lithium and subsequent work-up displaced the acetyl group.

Reaction of the nitriles (82) and (132) with the lithium alkyl afforded the corresponding imines (205) and (206) as gums. Hydrolysis, cyclisation and aromatisation was effected by heating these crude products with 20% acetic acid on a steam bath. The corresponding ellipticines (202) and (203) were obtained as yellow needles from chloroform. The ultra-violet and infra-red spectra of these compounds are, as expected, very similar to those of the parent alkaloid. Pmr spectra were taken in trifluoroacetic acid since both

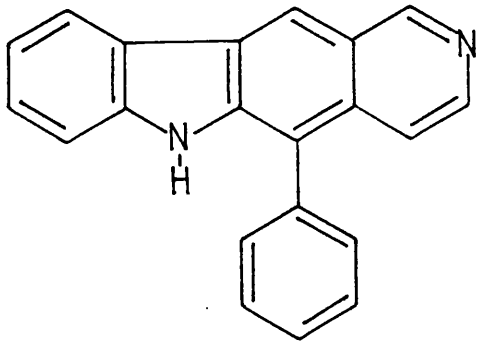


Printed in U.K.
Chart No. 4H-C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bladlow Ridge, High Wycombe, Bucks.

compounds possess only limited solubility in most organic solvents. The spectra show the butyl group signals as three proton triplets at δ1.1 ppm, four proton multiplets at 1.8 ppm and two proton, broadened triplets at 3.5 ppm. The spectrum of 5-butylellipticine shows a three proton singlet at 3.3 ppm while the C-11 proton of the demethyl derivative appears as a singlet at 8.8 ppm. The signals arising from the aromatic protons consist of three proton multiplets centred at δ7.5 and 8.3 ppm, while one proton doublets, ($\underline{J}$=7H_z), appear at lowest field, around 9.4 ppm. Decoupling experiments show that these doublets are not coupled to any other signals in the spectrum. Somewhat concerned, we ran a spectrum of ellipticine in trifluoroacetic acid and were relieved to observe the same low-field doublet which is therefore due to the interaction of the C-1 proton with the hydrogen atom effecting protonation of the pyridine nitrogen atom. In deuteriochloroform the spectrum of ellipticine displays the signal due to the C-1 hydrogen as a low-field singlet.

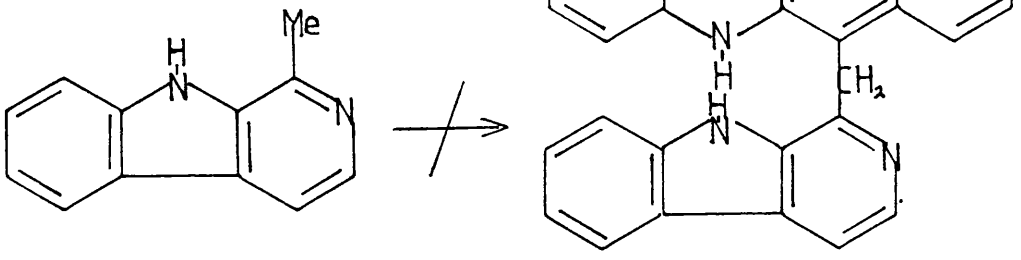
The mass spectrum of 5-butylellipticine displays a molecular ion peak at $\underline{m/e}$ 288 while the base peak, at $\underline{m/e}$ 245, indicates a facile loss of 43 mass units corresponding to a C_3H_7 group. The mass spectrum of the 11-demethyl analogue similarly shows a molecular ion peak at $\underline{m/e}$ 274 with the base peak at $\underline{m/e}$ 231.

Sufficient quantities of both compounds were prepared for a preliminary investigation into their pharmacological activity. We considered that it would not be profitable to synthesise a whole series of alkyl derivatives until we obtained an evaluation of the anti-cancer activity of the 5-n-butyl compounds. We decided, instead, to explore the scope of the alkylation reaction and to this end the nitrile (132) was treated with an excess of phenyl lithium. Once again a brown gum was obtained and this was heated with 20% acetic acid as before to give a fluorescent yellow solution. On cooling



(207)

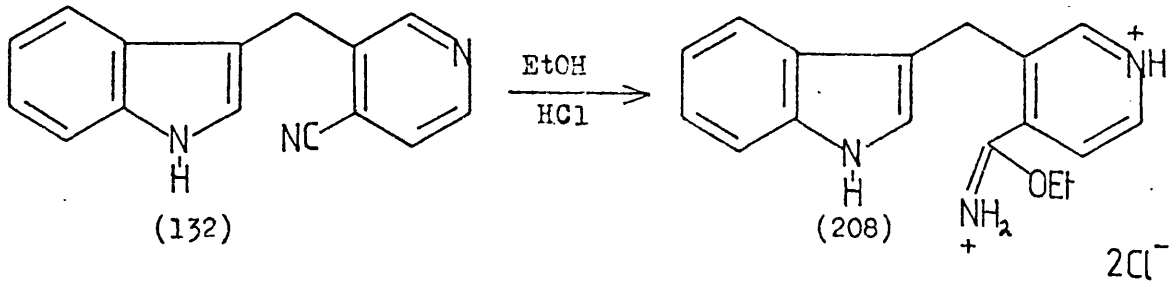
(132) +



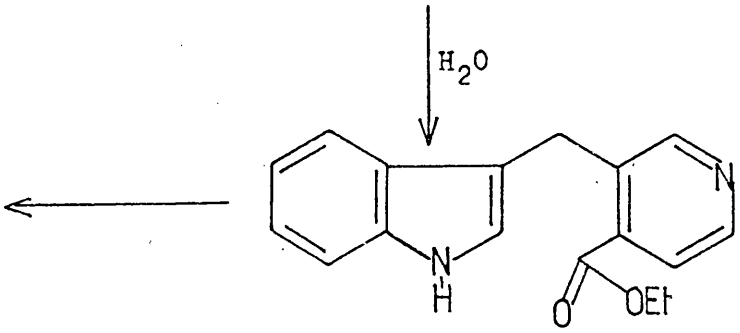
colourless prisms separated which were collected by filtration but were subsequently proved to be simply the acetate salt of the starting material. Basification of the remaining solution followed by extraction with chloroform afforded a gum from which further quantities of the nitrile (132) were isolated. The residue was dissolved in a little warm ethanol and on standing pale yellow platelets separated. The ultra-violet spectrum of this material shows a characteristic trace while pmr and precision mass measurement confirmed that we had isolated 5-phenyl-11-demethyl-ellipticine (207). The pmr spectrum (d^6DMSO) shows the indole N-H resonance as a broad singlet at 10.9 ppm while a singlet at 9.4 ppm corresponds to H-1. The C-11 proton resonates as a singlet at 8.9 ppm with complex signals at 8.3 and 7.5 ppm corresponding to the remaining protons. In the mass spectrum a molecular ion peak at m/e 294 is clearly displayed.

The yield of the ellipticine in this preliminary experiment was low due, no doubt, to the lower reactivity of phenyl lithium compared with alkyl lithiums. That the reaction proceeds at all suggests that steric hindrance is not an important factor as was previously thought when the nitrile (82) failed to react with methylmagnesium bromide. Although we did not optimize conditions it is probable, therefore, that more forcing conditions would prove more expeditious.

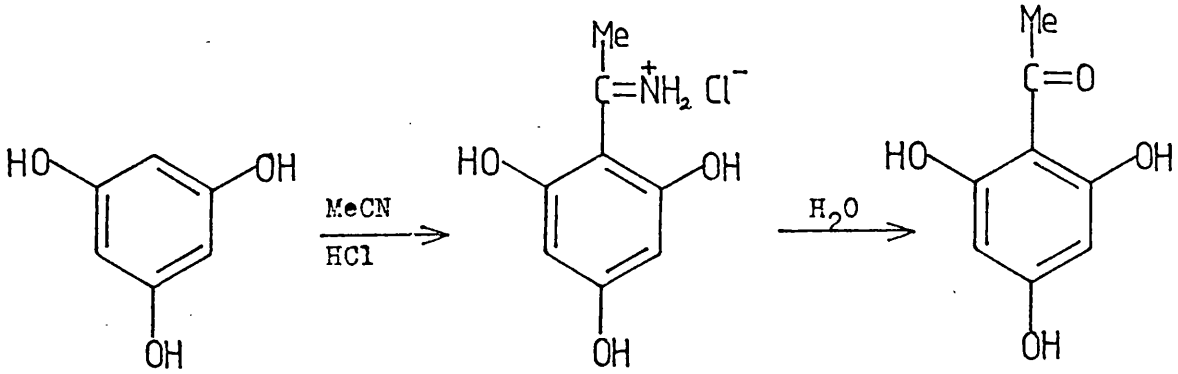
A rather more speculative reaction between the nitrile (132) and the anion of 1-methyl-β-carboline returned only starting materials presumably because, in this case, the size of the nucleophile is such that steric factors do play a moderating role. The choice of the anion, generated by treatment with n-butyl lithium, could, retrospectively, have been better since there are two acidic sites present in this molecule.



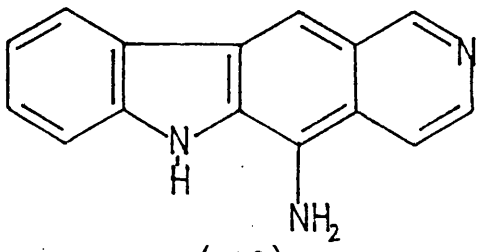
(132) (208)



(209)



(210) (211) (212)



(213)

We next investigated the synthetic possibilities offered by the reaction of (132) with hydrogen chloride. We have employed the Pinner reaction,[77] that of a nitrile with an alcohol in the presence of hydrogen chloride, in the preparation of ethylacetimidate hydrochloride (118) (page 23). We felt that a similar reaction on (132) to give the imidate (208) would allow us scope for cyclisation since the ester (209) should be readily available after hydrolysis. If, during the Pinner reaction, the temperature rises much above 0°C the corresponding amide is obtained and this suggested a possible route to the carboxylic acid.

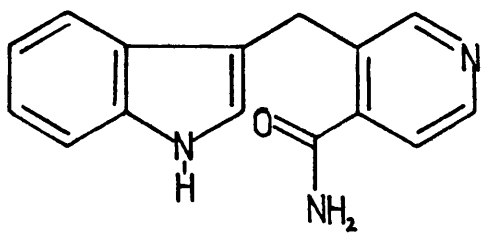
We decided first, however, to attempt a Hoesch-type reaction[78] on (132). Nucleophilic attack by activated aryl systems on the carbon atom of the nitrile function is well known for example, phloroglucinol (210) gives the ketimine (211) on treatment with hydrogen chloride in the presence of anhydrous zinc chloride. Subsequent hydrolysis to the acetophenone derivative (212) is effected by simply heating (211) in water. With our system we envisaged the formation of an amino derivative which, as well as being of interest in its own right, we hoped to use as an intermediate in our attempts to prepare the 5-hydroxyl compound.

The nitrile (132) and zinc chloride, in dry THF at -20°C, were treated with hydrogen chloride gas. A red precipitate separated immediately and the mixture was stirred for two hours when the solid was collected by filtration. The ultra-violet spectrum of this material is rich in detail, showing maxima at 224, 245, 292, 320, 333 and 350 (infl.) nm. The trace is similar to that characteristic of the pyrido (4,3-b)carbazoles except several absorptions are shifted to longer wavelengths. In the infra-red spectrum there are a series of finely split bands from 3300 to 3000 cm^{-1} while several weak absorptions are apparent between 2700-2650 cm^{-1}. A pair of medium intensity bands are situated at 1655 and 1635 cm^{-1} and there is a

stronger band, with a shoulder, at 1610 and 1600 cm^{-1} respectively. The pmr spectrum of this material was disappointing, in that it was poorly resolved, but the most interesting feature is the absence of any signals above 5.9 ppm. This suggests that cyclisation and subsequent aromatisation had occurred since it is most unlikely that signals due to methylene protons under these circumstances would resonate below 6 ppm. The spectrum consist of two broad signals at 12.3 and 10.9 ppm while the remaining protons, numbering eight, resonate between 8.4 and 6.4 ppm. The signals at lowest field exchange on treatment with deuterium oxide as does a broad resonance at 6.5 ppm. We tentatively conclude that this compound is 5-aminoellipticine (213) and we determined to substantiate this view. Despite being somewhat involatile in the mass spectrum this material shows a cluster of peaks at m/e 235, 234, 233, 232 and 231 with another at m/e 218.

Attempts to obtain a crystalline sample of this material were unsuccessful but when added to water it dissolved to give a fluorescent yellow solution. Extraction with organic solvents, after a few minutes of heating on a steam-bath, proved unproductive and so the mixture was neutralised with dilute sodium bicarbonate solution. Extraction gave yellow coloured organic layers but on evaporation only dark, intractible residues remained. We spent a considerable amount of time trying to isolate a crystalline derivative of this intriguing substance but without success. When treated with acetic anhydride, for example, a dark green solid was obtained but we were unable to characterise this material.

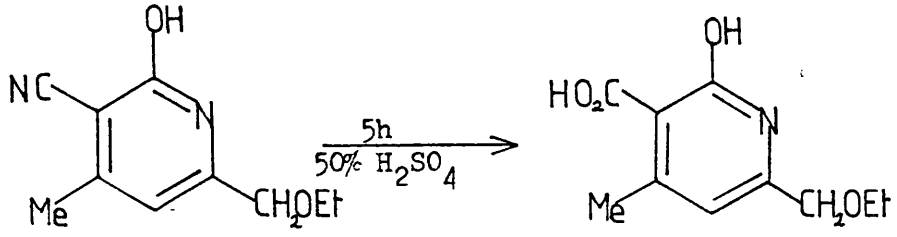
At this stage we felt, with time growing short, that we could not expend any more effort on these products. It is hoped that future work in this laboratory will prove more successful and a



(215)

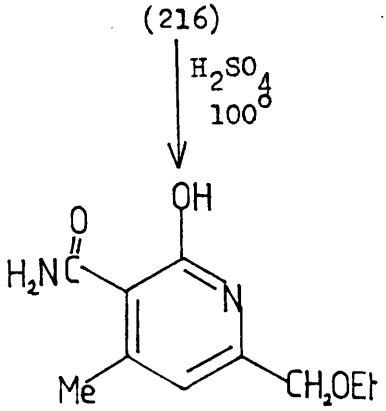
5-aminoellipticine will be isolated. This compound should prove to be a versatile intermediate in further synthetic studies.

To bring the work described in this thesis to an end we attempted once more, to effect the hydrolysis of the 4-cyanopyridine (132). As mild acid conditions give rise to the formation of the azaindene (160) we decided to focus our attention on the use of basic conditions. Previously, for example on the nitrile (128), we had used bench dilute sodium hydroxide solution but on this occasion we decided to use a minimum amount of water with three mol equivalents of potassium hydroxide. However, when the nitrile (132) was heated under these conditions a yellow mixture was obtained with a considerable amount of solid material remaining undissolved. Since previous work indicated that harsh conditions give rise to complex mixtures we decided to add a little methanol both to lower the temperature of reflux and to dissolve the solid. After a short period the mixture dissolved to give, after about two hours, an almost colourless solution. TLC analysis showed that no starting material remained and the presence of only one, slow moving component (5%MeOH/$CHCl_3$) was noted. On cooling a white solid separated which was collected by filtration. The ultra-violet spectrum of this substance is similar to that of the starting nitrile as is the pmr spectrum except that the resonance of the pyridine C-5 proton is shifted up-field to 7.4 ppm from 7.65 ppm. There is, additionally, a broad, indistinct signal at 7.8 ppm corresponding to two protons which may be removed on deuteration. This evidence suggested that the product was, in fact, the acid amide (215). The infra-red spectrum confirmed this deduction showing several absorptions above 3000 cm^{-1}. A pair of sharp bands appear at 3375 and 3320 cm^{-1} together with two more, less distinct absorptions at 3300 and 3110 cm^{-1}. The last of these bands is


OH
NC
N
Me
CH2OEt
5h
50% H2SO4
OH
HO2C
N
Me
CH2OEt

(216)

(217)


H2SO4
100°
OH
O
H2NC
N
Me
CH2OEt

(218)

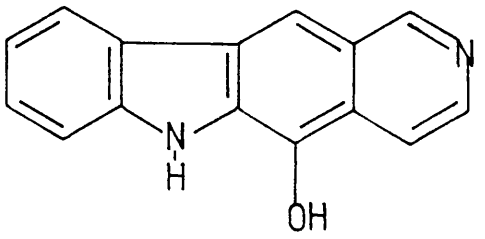
probably due to indole N-H stretching while the remainder are characteristic of amide N-H stretching. A carbonyl band appears at 1690 cm^{-1} while there are several absorptions in the 1620-1590 cm^{-1} region.

The isolation of the amide rather than the acid is not a surprise since the hydrolysis of pyridine nitriles,[79] especially hindered ones, often requires the use of forcing conditions and that reaction frequently proceeds only as far as the amide[80]. The nitrile (216), for example, when heated for five hours with 50% sulphuric acid gave only 5-10% of the acid (217) along with substantial quantities of decarboxylated product and starting material. Treatment with fuming sulphuric acid at 10° only cleaves the ether function while at 100°C a low yield of the amide (218) is obtained.[81]

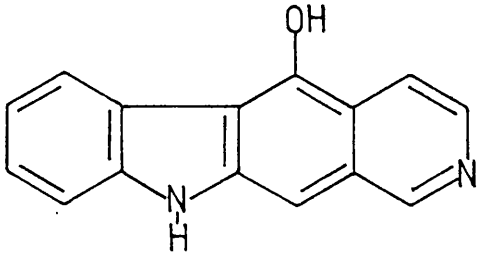
It now seems clear that in our case the use of mild alkaline conditions were just not forcing enough while the use of sodium hydroxide in boiling ethylene glycol or hot, 50% sulphuric acid served to effect partial hydrolysis but also caused some decarboxylation to occur. It has been observed that although pyridine nitriles may be hydrolysed under both acid and alkaline conditions the latter is generally more difficult while there is a greater tendency towards decarboxylation under acidic conditions. It has also been found that pyridine carboxamides may be converted to the corresponding acids using both hot acid and alkaline conditions[82] while the use of nitrous acid has also found favour since it is relatively mild.

We found that treatment of the nitrile (132) with potassium hydroxide in aqueous methanol for longer periods gave mainly the amide (215) but with increasing amounts of other products.

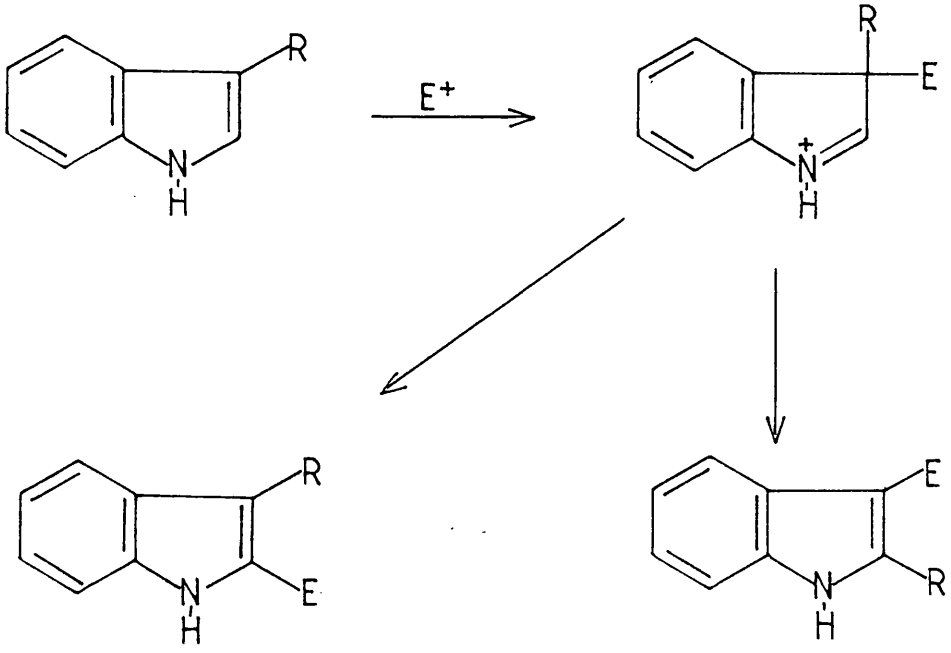
The amide (215) was heated with 12% sulphuric acid to give an orange solution from which yellow needles separated on cooling. We at first suspected that this material might be merely an amide



(219)

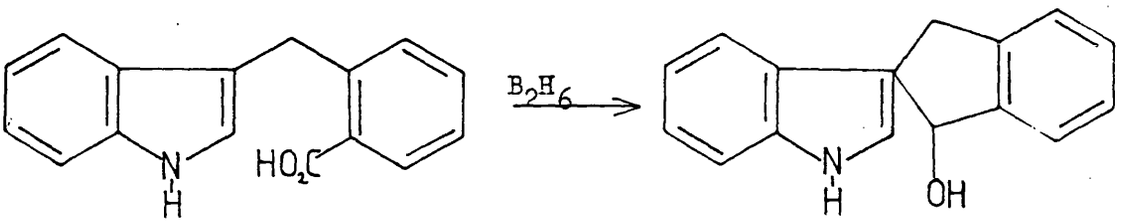


(220)

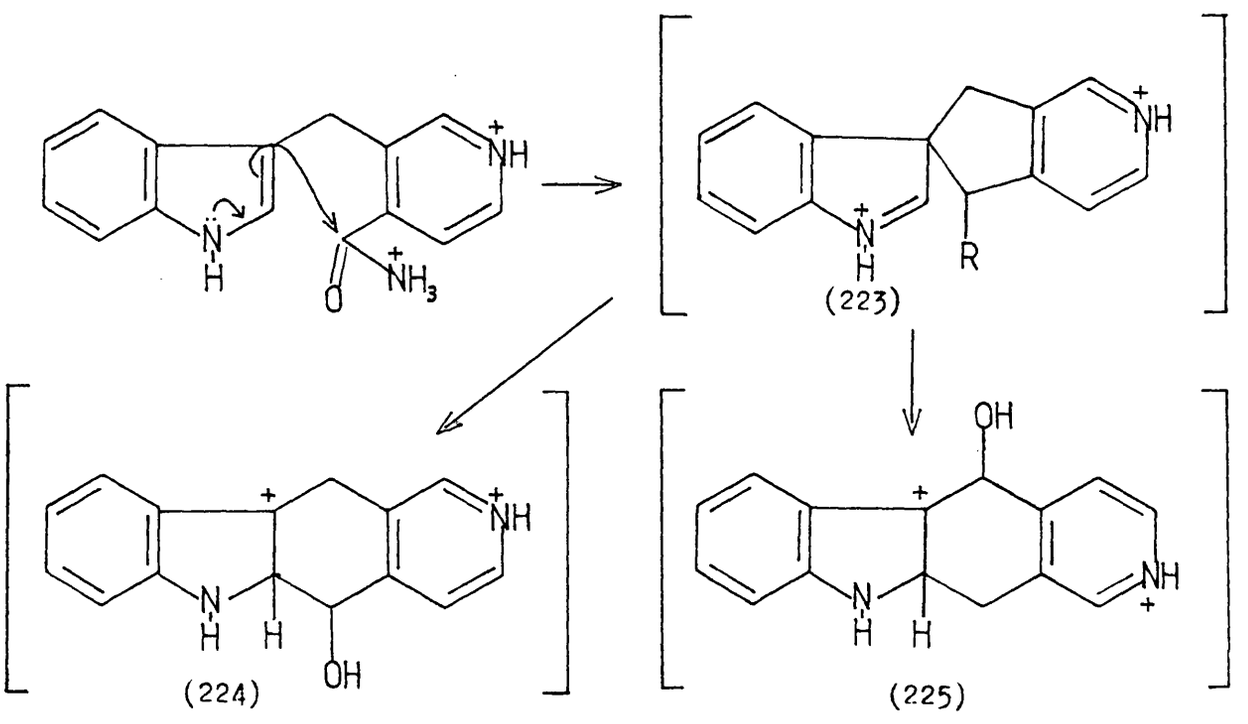


salt or the carboxylic acid but inspection of the infra-red spectrum dissuades us from either of these possibilities. There is no evidence of a carbonyl absorption with only two weak bands at 1640 and 1610 cm^{-1}. At the higher frequency end of the spectrum there is a broad band stretching from 3350-3150 cm^{-1}. The ultra-violet spectrum of this product bears similarities to that of the compound isolated from the Hoesch reaction and is again rich in detail. There are absorption maxima at 214, 226 and 245 nm, while a series of more intense absorptions occur at 275, 286, 297 and 308 nm. Finally, there are two bands of lower intensity at 352 and 362 nm. The addition of base causes the bands of strongest intensity to shift to slightly lower wavelengths. The pmr spectrum in d^6DMSO shows one, broadened signal at 12.0 ppm while two, one proton singlets absorb at 10.0 and 9.1 ppm. A doublet (J=7Hz) at 8.8 ppm corresponds to one proton while another, similar signal (J=7Hz) is superimposed upon an additional signal at 8.6 ppm. This grouping is due to the resonance of two protons while a complex signal centred at 7.7 ppm is due to 4 protons. These data suggest that we had isolated either the 5-hydroxy compound (219) or the analogous 11-hydroxy derivative (220) since in the mass spectrum this material displays a molecular ion peak at m/e 234. Analysis results served to support these formulations but, as in the case of the azaindene (160), it is difficult to positively assign one structure on the basis of the spectral data.

The eletrophilic substitution of indoles has been extensively studied[83] and it has been suggested that substitution at C-3 is rapid, but reversible, while substitution at C-2 is slower but irreversible. The work of Jackson and colleagues[84] in the late sixties, however, served to demonstrate that electrophilic substitution at the 2-position of 3-substituted indoles is not a direct process but involves the formation of an intermediate indolenine which may then rearrange to



(221) (222)

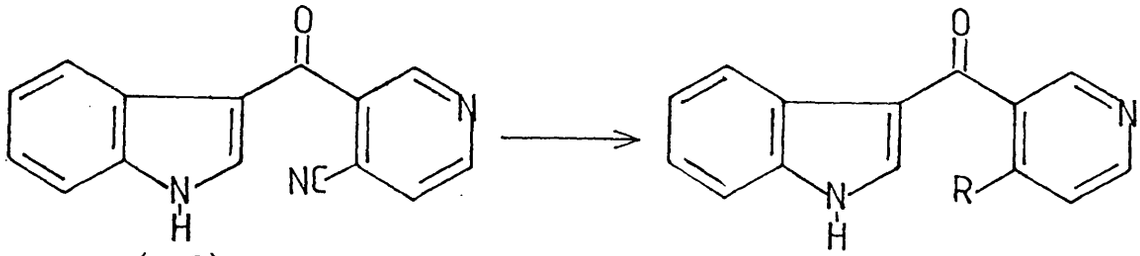


(219) (220)

give a 2,3-disubstituted indole. The alkylation of 3-alkylindoles, for example, has been shown[85,86] to give 3,3-dialkylindolenines which rearrange to 2,3-dialkylindoles and it was noted that, in general, the higher alkyl group was the one that migrated. In many instances the 3,3-disubstituted indolenine may have a spirocyclic structure. During the course of a reaction involving the reduction of the carboxybenzylindole (221) with diborane the spirocyclic indolenine (222) was isolated as a stable, crystalline solid. It is significant that cyclisation at the 3-position, leading to the formation of this compound containing a strained, spiropentene ring, is still favoured rather than at the 2-position of the indole nucleus.

In our case electrophilic substitution at the 3-position again leads to a spiropentene intermediate (223) (c.f. in the case of the azaindene where a spirobutene ring is required). Subsequent rearrangement leads to the formation of one or other of the two carbonium ions (224) or (225) which then aromatise to give the isolated product. If loss of the ammonia unit occurs first it is possible that a spirocyclic carbonyl intermediate is involved. In any event it is not clear which of the two bonds to the indole 3-position is the more likely to break and it will be necessary for further work to be carried out before a definite conclusion may be drawn.

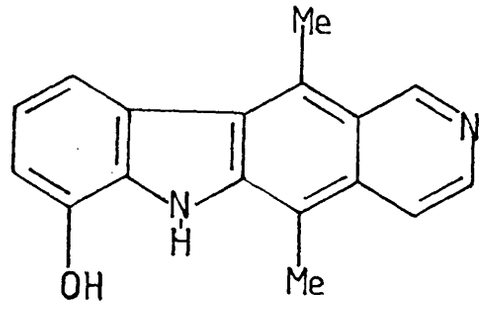
It was found that if the crude, acidic solution was neutralised and extracted with chlororform an amorphous yellow solid was obtained. This material proved to be relatively unstable since attempts to obtain a crystalline sample led to the recovery of dark residues. Acetylation attempts were also unsuccessful, affording intractable tars.



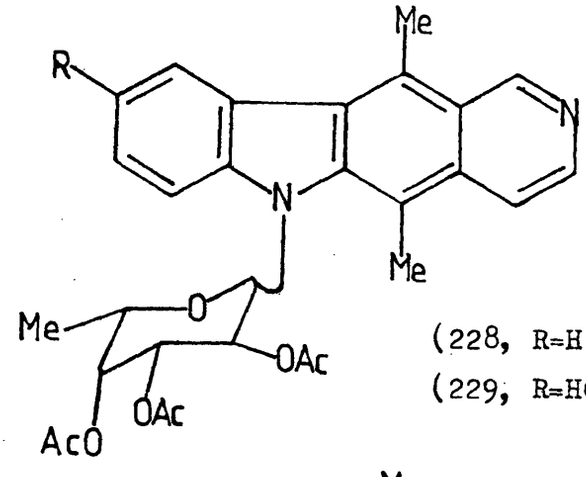
(128)

(130, R=CO_2H)

(226, R=$CONH_2$)

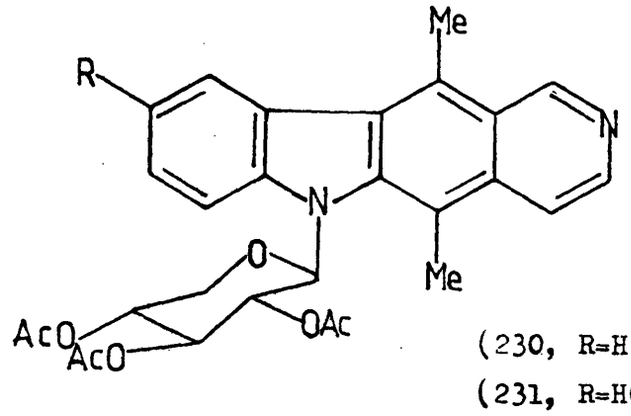


(227)



(228, R=H)

(229, R=HO)



(230, R=H)

(231, R=HO)

Despite these difficulties it now seems apparent that a productive route to hydroxylated ellipticine derivatives is feasible. We found, for example, that hydrolysis of the carbonyl bridged nitrile (128) using the conditions described above, gives a mixture of the corresponding acid (130) and acid amide (226). Work is now in progress designed to employ these compounds in the preparation of the 5,11-dihydroxyl derivative (131). Similarly, it should prove possible to repeat the procedure on the nitrile (82) to give 5-hydroxyellipticine itself.

The importance of the hydroxyl function in conferring anti-tumour activity to the pyrido(4,3-b)carbazoles has recently been further demonstrated by French workers[87-89]. They have shown that in rats ellipticine is metabolised, principally to the 9-hydroxy derivative, and it is feasible, therefore, that the anti-tumour properties previously associated with the alkaloid itself, are in fact due to this metabolite. A small proportion of the 7-hydroxy compound (227) has also been indentified in excretion products but this compound has since been synthesised[87] and found to be inactive.

Synthetic work on ellipticine derivatives is becoming more diverse, for example, the nucleoside derivatives (228-231) have recently been prepared.[90] However, it is clear that much work remains to be done,both to determine the most active compounds in the ellipticine series and more generally, to discover more effective chemotherapeutic agents for the treatment of human cancer. It is hoped that the work described in this thesis may prove helpful in this goal.

EXPERIMENTAL

All melting points were recorded on a Gallenkampf apparatus and are uncorrected. Ultra-violet spectra were recorded for 95% ethanolic solutions on a Perkin-Elmer 402 ultra-violet and visible spectrophotometer. Infra-red spectra were taken as Nujol mulls or as liquid films on either a Perkin-Elmer 237 or 197 instrument. Proton magnetic resonance spectra were recorded on either a Varian EM360 or a J.E.O.L. PS100 instrument at 60MHz or 100MHz respectively. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on an A.E.I.MS12 instrument at 12 and 70 eV.

Unless otherwise stated all organic solutions were dried over anhydrous magnesium sulphate and evaporated *in vacuo*.

1-(2-Oxoindol-3-ylidene 3-pyridyl)ethane (89)

A solution of oxindole (88) (3.3. g) and 3-acetylpyridine (87) (3.0 g), in benzene (75 ml), was refluxed for six hours with pyrrolidine (1.7 g) under a Dean-Stark trap. Removal of the solvent left a dark oil from which red prisms separated on cooling. These were collected by filtration, washed with a little benzene and dried (4.5 g, 77%).

m.p. 163-164°C, (lit[47] 164-165°C),

U.V. λ max 220, 257 and 305 nm,

I.R. ν max 3200 (NH), 1700 (CONH) and 1620 (C=C) cm^{-1},

P.M.R. δ ($CDCl_3$) 10.05 (1H, s, N-H), 8.75-8.50 (2H, complex, H-2 and H-6), 7.70-6.05 (6H, complex, H-4, H-5, H-4', H-5', H-6' and H-7') and 2.77 (3H, s, CH_3) ppm,

M.S. m/e (rel. int. %) 236 (M^+, 100) and 221 (80).

(Found: C, 76.2; H, 5.2; N, 11.6. Calc. for $C_{15}H_{15}N_2O$ C, 76.2; H, 5.1; N, 11.8%).

1-(2-Oxoindol-3-ine 3-pyridyl)ethane (90)

A solution of the oxindolylidene (89) (2.0 g), in 50% aqueous ethanol (50 ml) at 60°C, was treated with sodium borohydride (2.0 g) and stirred for one hour when the yellow mixture was evaporated to dryness. The residue was partitioned between water (20 ml) and chloroform (50 ml) and the organic phase separated, washed with brine, dried and evaporated to give a yellow gum (2.0 g, 100%).

U.V. λ max 208, 255 and 261 nm,

I.R. ν max 3160 (NH) and 1715 (CONH) cm^{-1},

P.M.R. δ ($CDCl_3$) 9.55 (1H, s, N-H), 8.50-8.16 (2H, complex, H-2 and H-6), 7.70-6.65 (6H, complex, H-4, H-5, H-4', H-5' H-6', and H-7'), 3.75-3.55 (2H, complex, CH-CH) and 1.56-1.20 (3H, dx2, CH_3) ppm.

M.S. m/e (rel. int. %) 238 (M^+, 38), 133 (82), 106 (100) and 77 (56),

(Found: C, 75.4; H, 7.3; N, 11.9. Calc. for $C_{15}H_{17}N_2O$ C, 75.6; H, 7.1; N, 11.8%).

Attempted reduction of the oxindole (90)

(a) Phosphorus pentasulphide

Phosphorus pentasulphide (prepared by slowly heating yellow phosphorus with carbon disulphide in napththalene to 170-190°C) was heated to 110°C for three hours with the oxindole (90) (1.0 g) in pyridine (30 ml). The mixture was cooled, when water (40 ml), was added. Extraction with benzene (2 x 40 ml) gave a red oil which was dissolved in ethanol (20 ml) and heated under reflux for one hour with Raney nickel (2.0 g). The mixture was cooled, filtered and evaporated to give an orange gum which was dissolved in a little benzene but could not be induced to crystallize. TLC, infra-red and pmr analysis confirmed that we had isolated only starting material (0.82 g).

Longer periods of heating with P_4S_{10} gave similar results.

(b) Sodium acetoxyborohydride

Acetic acid (6.0 g, 0.1M), in dioxan (10 ml), was added dropwise to a stirred suspension of sodium borohydride (3.78 g, 0.1M) and the oxindole (90) (2.4 g, 0.01M), in dioxan (20 ml), at 10°C. When the addition was complete the mixture was heated under reflux for two hours when the dioxan was removed by evaporation. The residue was treated with water (10 ml), then sodium bicarbonate solution (20 ml) and finally extracted with chloroform (2 x 30 ml). The combined extracts were washed with sodium bicarbonate solution, dried and evaporated to afford a yellow gum (2.1 g) which was identified as the starting oxindole (90).

Heating for longer periods and the use of trifluoroacetic acid yielded only starting material.

(c) Diborane.

A solution of the oxindole (90) (1 g), in dry T.H.F. (50 ml), was stirred while a 3 molar excess of a solution of diborane (0.1M) in T.H.F. was added dropwise. The mixture was gently refluxed for one hour and allowed to cool when 6N hydrochloric acid (20 ml) was carefully added. The T.H.F. was removed by evaporation and the residue partitioned between sodium bicarbonate solution and chloroform. The organic phase was separated, washed with brine, dried and evaporated to give starting material. Similar results were obtained when larger excesses of reducing agent were employed or when the period of heating was extended.

(d) Lithium aluminium hydride.

The oxindole (90) (1.0 g), in dry T.H.F. (25ml) under a nitrogen atmosphere, was stirred with lithium aluminium hydride (0.16g, 4 mol. equiv.) for one hour at room temperature. Work-up yielded a yellow gum which was shown (i.r. and p.m.r.) to be starting material.

When the reaction was repeated, but in refluxing T.H.F., dark gums were isolated which could not be characterised, along with some starting material.

3-(1-Hydroxyethyl)pyridine (113)

3-Acetylpyridine (50 g), in ethanol (200 ml), was stirred while sodium borohydride was added portionwise and the temperature kept below 30°C by means of an ice-bath. When a constant ultra-violet trace was obtained excess reducing agent was destroyed by the addition of water (25 ml). The mixture was evaporated to low bulk and extracted with chloroform (3 x 50 ml). The extracts were combined, dried and evaporated to give a yellow oil which was distilled under reduced pressure to give a colourless product (38 g, 74%).

b.p. 90°C(0.3 mm Hg),

U.V. λ max 255, 261 and 268 nm,

I.R. ν max 3350 br (O-H) and 1410 (OH) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.55 (1H, bs, O<u>H</u>), 8.42 (1H, s, H-2), 8.25 (1H, m, H-6), 7.73 (1H, m, H-4), 7.23 (1H, m, H-5), 4.92 (1H, q, <u>J</u>=9Hz, C<u>H</u>) and 1.52 (3H, d, <u>J</u>=9Hz, C<u>H</u>$_3$) ppm.

<u>3-(1-Chloroethyl)pyridine (78)</u>

The alcohol (113) (20 g), in dry benzene (50 ml), was maintained at 0-5°C while thionyl chloride (20 g) was added dropwise. A white gum soon separated and the mixture was stirred, mechanically, for one hour. The benzene and thionyl chloride were removed by vacuum evaporation at 10°C and the residue dissolved in water (50 ml). The free pyridine was liberated by the careful addition of solid sodium bicarbonate and extraction with ether afforded an unstable pale yellow oil (18.5 g 80%).

I.R. ν max 650 (CH-Cl) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.45 (1H, s, H-2), 8.30 (1H, m, H-6), 7.70 (1H, m, H-4), 7.30 (1H, m, H-5), 5.10 (1H, q, <u>J</u>=9Hz, C<u>H</u>) and 1.61 (3H, d, <u>J</u>=9Hz, C<u>H</u>$_3$) ppm.

<u>Indolylmagnesium bromide</u>

To dry magnesium turnings (2.3 g, 0.1M) and ether (50 ml), was added 5 ml of a solution of bromoethane (10.9g)in anhydrous ether (50 ml) to initiate the reaction. The remaining solution was added at a rate sufficient to maintain reflux. The mixture was stirred for 30 minutes after the addition was complete and then chilled in an ice-salt bath when indole (10.5 g, 0.09M), in dry ether (50 ml), was added dropwise. After the addition the two-phase system was allowed to warm to room temperature and stirred for a further 30 minutes. This suspension of indolylmagnesium bromide was then used directly.

Ethyl acetimidate hydrochloride (118)

A solution of absolute ethanol (97 g) and dry acetonitrile (82 g) in anhydrous ether (125 ml) was cooled to 0°C while hydrogen chloride gas was passed through. When 1 mol equivalent of hydrogen chloride had been absorbed (approx 3 hr.) the mixture was evaporated *in vacuo* to afford a colourless, crystalline mass which was washed with ether and dried in a vacuum desicator (226 g, 92%).

m.p. 299°C,

I.R. ν max 1640 (C=$\overset{+}{N}$) cm^{-1},

P.M.R. δ (d^6acetone) 12.33 and 11.40 (2H, 2xbs, $\overset{+}{N}\underline{H}_2$), 4.55 (2H, q, J=8Hz, $C\underline{H}_2CH_3$), 2.58 (3H, s, $C\underline{H}_3$) and 1.52 (3H, t, J=8Hz, $CH_2C\underline{H}_3$) ppm.

1-Ethoxy -1-oximidoethane (119)

Ethyl acetimidate hydrochloride (118) (30 g) was shaken vigorously with a cooled solution of potassium carbonate (67 g, 2 mol equiv.) in water (200 ml) for 10 minutes. The organic layer was separated and the aqueous phase extracted with ether (3 x 100 ml) when the combined organic extracts were washed with water (2 x 50 ml). A solution of hydroxylamine hydrochloride (18 g) in water (60 ml) was then added and the mixture stirred vigorously for 15 minutes. The ether layer was separated and the aqueous phase was extracted with more ether (2 x 75 ml). The ethereal extracts were combined, washed with water (2 x 50 ml), dried and evaporated to yield a colourless oil which on cooling afforded a solid (15.6 g, 74%).

m.p. 17-18°C,

I.R. λ max 3600-3250(OH), 1665 (C=N), 1300 (OHdef.) and 1050 (OHdef.)cm^{-1}.

Mesitylene sulphonyl chloride (121)

Mesitylene (120) (50 g) was added dropwise, with stirring

and cooling, to chlorosulphonic acid (97.3 g, 3 mol equivalents). The temperature was kept below 20°C and the dark mixture stirred for one hour when it was carefully poured onto crushed ice (300 g). The separated solid was dissolved in carbon tetrachloride (50 ml) while the remaining solution was extracted with further quantities of organic solvent (2 x 100 ml). The organic extracts were combined, washed with aqueous sodium carbonate (3 x 100 ml), dried and evaporated to yield a pale yellow solid which crystallized from petroleum ether as colourless needles (84.2 g, 93%).

m.p. 50-51°C.

I.R. λ max(Nujol) 1600(Ar), 1580(Ar), 1360(SO_2), 1180(SO_2) 1170(SO_2), 850, 780 and 740 (1, 2, 3, 5-substitution) cm^{-1},

P.M.R. δ($CDCl_3$) 7.16 (2H, s, aryl protons), 2.73 (6H, s, 2xCH_3) and 2.73 (1H, s, CH_3) ppm.

Ethyl-O-mesitylsulphonylacetohydroxamate (122)

1-Ethoxy-1-oximidoethane (119) (20 g) and triethylamine (21.7 g, 1.1 mol equiv.) in dimethylformamide (100 ml) at 0°C were stirred while mesitylene sulphonyl chloride (121) (42.4 g) was added portion-wise over 30 minutes. When the addition was complete the mixture was stirred for a further hour at 10-15°C when it was poured onto crushed ice (500 g). Vigorous scratching caused the separated oil to solidify and the material was collected by filtration and washed with a little petroleum ether. The solid was dried between filter papers and quickly stored in a freezer below -20°C. since in the past this material has proved to be dangerously unstable. (45 g, 80%).

I.R. ν max 1645(C=N), 1360(asy SO_2O) and 1180(sy. SO_2O) cm^{-1}.

O-Mesityl sulphonyl hydroxylamine (MSH) (80)

Ethyl-O-mesitylsulphonylacetohydroxamate (122) (10 g) was added to 70% perchloric acid (30 ml) and warmed to 35°C to aid dissolution. The mixture was stirred at room temperature for 20 minutes

when it was poured onto crushed ice with stirring. After 2 minutes the precipitated solid was filtered, washed well with cold sodium bicarbonate solution and then chilled water. The solid was dissolved in ether and the residual water separated. The ether layer was dried ($MgSO_4$) and evaporated below 20°C to afford a colourless solid (6.2 g, 82%). This material may be stored for about one month at -20°C before appreciable deterioration occurs. At higher temperatures decomposition is much more rapid.

I.R. δmax 3270(NH_2) 3230(NH_2), 1365 and 1170(SO_2O)cm^{-1}.

3-(1-(3-Pyridyl)ethyl)indole (79)

(a) From indolylmagnesium bromide and 3-(1-chloroethyl)pyridine (78).

A suspension of indolylmagnesium bromide (20 g, 0.09M) in anhydrous ether (150 ml) was cooled to -5°C when 3-(1-chloroethyl) pyridine (78) (6.4 g, 0.045M) was added. The mixture was stirred for two hours, allowed to warm to room temperature and then stirred for a further 48 hours. The dark product was cooled to 0°C and extracted with 2N hydrochloric acid (5 x 50 ml). The combined extracts were washed with ether and basified with dilute ammonium hydroxide solution when a white flocculate separated. Extraction with chloroform (4 x 100 ml) afforded a red gum which was triturated with ether whereupon colourless cubes slowly separated. The solid was collected by filtration, washed with ether and recrystallized from ethanol (1.8 g, 18%).

m.p. 173 °C (lit.[28], 173-174°C),

U.V. λmax 229, 270, 280 and 291 nm,

I.R. νmax 3130 (NH),1590 and 1580(Ar)cm^{-1},

P.M.R. δ($CDCl_3$) 9.58 (1H, bs, N-H), 8.66 (1H, d, J=2Hz, H-2) 8.45 (1H, dd, J=2Hz and J=6Hz, H-6), 7.70-6.95 (7H, complex, H-4, H-5, H-2', H-4', H-5', H-6' and H-7'), 4.50 (1H, q, J=8Hz, $C\underline{H}CH_3$) and 1.82 (3H, d, J=8Hz, $CHC\underline{H}_3$) ppm.

M.S. m/e (rel. int.%) 222 (M^+, 47) 207 (100) and 144 (20).

(Found: C, 81.1; H, 6.3; N, 12.5, Calc. for $C_{15}H_{14}N_2$ C, 81.1; H, 6.4; N, 12.6%).

(b) From indole and 3-acetylpyridine

Indole (14.6 g) was heated with 3-acetylpyridine (7.6 g) for 24 hours in refluxing acetic acid (60 ml). On cooling and basification with 5% sodium hydroxide solution a white solid precipitated. Filtration gave bis-1, 1-(indol-3-yl)-1-(3-pyridyl) ethane (20) as a cream coloured solid which crystallized from ethanol as colourless prisms (12.5 g, 59%).

m.p. 250-253°C (lit.[2] 253°C dec.),

U.V. λ max 225 and 241 nm,

I.R. ν max 3400 (NH) cm^{-1},

P.M.R. δ ($CDCl_3$/d^6DMSO). 12.00 (2H, bs, N-Hx2), 8.70 (1H, bs, H-2), 8.45 (1H, d, J=6Hz, H-6), 7.92-6.68 (12H, complex, remaining aromatic protons) and 2.35 (3H, s, CH_3) ppm.

M.S. m/e 337 (M^+, 37) and 322 (100).

(Found: C, 82.0; H, 5.6; N, 12.4. Calc. for $C_{23}H_{19}N_3$ C, 81.9; H, 5.6; N, 12.5%).

The bis-indolyl product (20) (10 g) and potassium hydroxide (0.3 g), in a vacuum distillation apparatus, were gently heated (at 0.1 mm Hg) until about half of the reaction mixture had distilled over. The products were combined and chromatographed on silica eluting with 5% methanol in dichloromethane. The first fractions contained indole and then 1-(indol-3-yl)-1-(3-pyridyl)ethane (204), as colourless prisms, was obtained (2.8 g, 43%).

m.p. 135°C, (lit.[66] 136-138°),

U.V. λ max 242 and 274 nm,

I.R. ν max 3140 (N-H), 1620 (C=CH_2) and 1600 (Ar) cm^{-1},

P.M.R. δ ($CDCl_3$) 9.30 (1H, bs, N-H), 8.82 (1H, d, J=2Hz, H-2), 8.62 (1H, dd, J=2Hz and J=5Hz, H-6), 7.88-6.90 (7H, complex, H-4, H-5, H-2', H-4', H-5', H-6' and H-7') and 5.62 (2H, 2xd, J=2Hz, CH_2) ppm.

M.S. m/e (rel. int.%) 220 (M^+, 100), 219 (62), 218 (18) and 205 (29).

(Found : C, 81.6; H, 5.7; N, 12.6; Calc. for $C_{15}H_{12}N_2$ C, 81.8; H, 5.5; N, 12.7%)

The ethene (204) (3.5 g) was dissolved in ethanol and catalytically hydrogenated using Pd/C catalyst (0.5 g). Chromatography on silica afforded (79) as colourless prisms (2.9 g, 82%).

1-Acetyl-3-(1-(3-pyridyl)ethyl)indole (79, R=Ac).

The indole (79) (2.1 g) was heated with triethylamine (2 ml) in boiling acetic anhydride (15 ml) for one hour after which time the solution was evaporated to dryness and the residue partitioned between sodium bicarbonate solution (15 ml) and chloroform (50 ml). The organic layer was separated, washed with brine, dried and evaporated to yield a cream-coloured solid which crystallized from ethanol as colourless prisms (2.2 g, 88%).

m.p. 123°C (lit.[28] 123-124°),

U.V. λ max 224, 257 and 316 nm,

I.R. ν max 1700 (C=O) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.55 (1H, d, J=2Hz, H-2), 8.48-8.20 (2H, complex, H-6 and H-7'), 7.42 (1H, dt, J=2Hz and J=8Hz, H-4), 7.29-6.90 (5H, complex, H-5, H-2', H-4', H-5' and H-6'), 4.20 (1H, q, J=8Hz, $CHCH_3$), 2.50 (3H, s, $COCH_3$) and 1.58 (3H, d, J=8Hz, $CHCH_3$) ppm.

M.S. m/e (rel. int. %) 264 (M^+, 35), 222 (30), 207 (100) and 144 (17).

(Found: C, 77.2; H, 6.0; N, 10.8; Calc. for $C_{17}N_{16}N_2O$ C, 77.3; H, 6.1; N, 10.6%).

1-Acetyl-3-(1(4-cyanopyrid-3-yl)ethyl)indole (82).

The N-acetylindole (79, R=Ac) (4.7 g), in dichloromethane (20 ml), was cooled to 0°C when O-mesitylsulphonylhydroxylamine (80) (3.8g, 1 mol equiv.) in dichloromethane (15 ml), was added. The solution was stirred for one hour, ether (100 ml) added and a pale brown oil separated. The solvents were decanted, the oil washed with ether (10 ml), then taken-up in cool water (35 ml) and treated with acetic anhydride. The mixture was stirred as aqueous 30% potassium hydroxide (27 ml) was added dropwise. After ten minutes the solution was made basic with potassium carbonate and extracted with chloroform. The organic phase was separated, washed with water, dried and evaporated, at low temperature, affording a colourless oil (m/e 321 (M^+, 28), 306 (15), 279 (13), 264 (46), 222 (33) and 207 (100)).

The oil (3 g), in boiling acetone (15 ml), was heated with methyl iodide (10 ml) for one hour when the solvents were removed to yield a yellow foam (4.1 g, 95%). (νmax, 3400 (N-H), 1710 (N-$COCH_3$), 1695 ($\overset{+}{N}$-$NCOCH_3$), 1615 (C=$\overset{+}{N}$) and 1605 (Ar) cm^{-1}, δ (d^6DMSO) 9.56 (1H, s, H-2), 9.20 (1H, bs, H-6), 8.83 (1H, bd, J=7Hz, H-4), 8.43-8.23 (2H, m, H-5 and H-7'), 7.95 (1H, s, H-2'), 7.58-7.12 (3H, m, H-4', H-5' and H-6'), 4.70 (1H, q, J=8Hz, C$\underline{H}CH_3$), 3.76 (3H, s, N-$C\underline{H}_3$), 2.70 (3H, s, $NCOC\underline{H}_3$), 2.31 (3H, s, $\overset{+}{N}$-$NCOC\underline{H}_3$) and 1.79 (3H, d, J=8Hz, $CHC\underline{H}_3$) ppm.
This product, dissolved in water (30 ml), was treated with ammonium chloride (0.95 g) and potassium cyanide (0.65 g). After stirring for one hour the mixture was extracted with chloroform (4 x 75 ml). The organic extracts were bulked, washed with water (3 x 100 ml), dried and evaporated to yield an oil which was dissolved in ethanol and irradiated with 'soft' ultra-violet light for 30 minutes. The ethanolic solution was then evaporated to low bulk and cooled when colourless prisms separated (1.8 g, 70%).

m.p. 110-112°C, (lit.[28] 111-112°),

U.V. λ max 229, 255 and 320 nm,

I.R. ν max 2235 (C≡N) and 1720 (C=O) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.60 (1H, s, H-2), 8.58 (1H, d, J=6Hz, H-6), 8.36 (1H, m, H-7'), 7.49-7.03 (5H, complex, H-4, H-2', H-4', H-5' and H-6'), 4.68 (1H, q, J=7Hz, $CHCH_3$), 2.64 (3H, s, $NCOCH_3$) and 1.82 (3H, d, J=7Hz, $CHCH_3$) ppm.

M.S. m/e (rel. int. %) 289 (M^+, 52), 247 (48) and 232 (100).

(Found : C, 74.7; H, 5.3; N, 14.6. Calc. for $C_{18}H_{15}N_3O$ C, 74.7; H, 5.2; N, 14.5%.

The corresponding indole N-H compound (82), obtained when the residues from the above irradiation experiment were chromatographed on basic alumina, possesses,

m.p. 117-119°C, (lit.[28] 118-119°),

U.V. λ max 228, 274 and 293 nm,

I.R. ν max 3130 (N-H), 2230 (C≡N) and 1585 (Ar) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.82 (1H, bs, N-H), 8.65 (1H, s, H-2), 8.55 (1H, d, J=6Hz, H-6), 7.52-6.95 (6H, complex, H-4, H-2', H-4', H-5', H-6' and H-7'), 4.74 (1H, q, J=8Hz, $CHCH_3$) and 1.80 (3H, d, J=8Hz, $CHCH_3$) ppm,

M.S. m/e (rel. int.%) 247 (M^+, 51), 232 (100) and 207 (21).

(Found: C, 77.8; H, 5.3; N, 17.0 Calc. for $C_{16}H_{13}N_3$ C, 77.7; H, 5.3; N, 17.0%).

Reaction of 3-(1-(4-cyanopyrid-3-yl)ethyl)indole (82) with dilute hydrochloric acid

The nitrile (82) (100 mgs) was heated in refluxing 2N hydrochloric acid (15 ml) for one hour when the solution was cooled and made neutral with dilute ammonium hydroxide solution. Extraction with chloroform yielded an orange gum which, by TLC, was shown to consist of three major components, a blue, fluorescent compound, Rf 0.25 and an orange component, Rf 0.22. Preparative column chormatography on silica allowed separation but we obtained very small amounts of material which we were unable to characterise.

Nicotinoyl chloride (125)

An anhydrous solution of nicotinoyl chloride in benzene was prepared as follows.

Finely ground, dry potassium nicotinate (32 g), in dry benzene (150 ml), was chilled in an ice-bath while oxalyl chloride (25 g) in benzene (50 ml) was added dropwise. The mixture was stirred for 30 minutes, brought to boiling over a further 30 minutes and maintained at reflux for a similar period. After cooling to -10°C the solution was used directly for reaction with Grignard reagents. (This procedure is reported [56] to effect an 80% conversion to the acid chloride).

Indol-3-yl 3-pyridyl ketone (126)

A suspension of indolylmagnesium bromide (61 g, 0.28M) in anhydrous ether (200 ml) was added, dropwise, to a mechanically stirred solution of nicotinoyl chloride (0.19M) at -10°C. The mixture was stirred overnight at room temperature when the organometallic complex was hydrolysed by the careful addition of saturated ammonium chloride solution (30 ml). The dense, yellow precipitate was filtered, washed with water and then ether, and recrystallized, twice, from ethanol to furnish the ketone as colourless leaflets. A small amount of additional material was obtained from the aqueous phase after basification and extraction with chloroform (29.2 g, 70%).

m.p. 210-211°C (lit.[28] 210-211°),

U.V. λ max 230, 258, 270 and 320 nm,

I.R. ν max 3150 (N-H), 1600 (C=O) and 1580 (Ar) cm^{-1},

P.M.R. δ (d^6DMSO) 12.10 (1H, bs, N-H), 9.05 (1H, d, J=2Hz, H-2) 8.80 (1H, dd, J=2Hz and J=5Hz, H-6), 8.50-7.92 (3H, complex, H-4, H-2', and H-4') and 7.81-7.12 (4H, complex, H-5, H-5', H-6' and H-7') ppm.

M.S. m/e (rel. int.%) 222 (M^+, 80), 144 (100) and 117 (60).

(Found: C, 75.7; H, 4.5; N, 12.7. Calc. for $C_{14}H_{10}N_2O$ C, 75.7; H, 4.5; N, 12.6%.)

If the temperature rises much above -10° during the addition of the indolyl Grignard reagent a substantial amount of 1-nicotinoylindol-3-yl 3-pyridyl ketone (133) is formed. This product shows a molecular ion peak at m/e 327 in the mass spectrum. The indole N-nicotinoyl function is readily displaced by the heating(133) in organic solvents (i.e. ethanol).

1-Acetylindol-3-yl 3-pyridyl ketone (134)

Indol-3-yl 3-pyridyl ketone (126) (9.2 g) was heated with boiling acetic anhydride (40 ml) for one hour when the mixture was evaporated to dryness. The residue was partitioned between sodium bicarbonate solution (30 ml) and chloroform (100 ml). The chloroform layer was separated, washed with water, dried and evaporated to yield a solid which was recrystallized from ethanol to give colourless leaflets (9.7 g, 89%).

m.p. 141°C,

U.V. λ max 212, 230, 252 and 309 nm,

I.R. ν max 1740 (N-Ac) and 1625 ($Ar_2C{=}O$) cm^{-1},

P.M.R. δ ($CDCl_3$) 9.05 (1H, d, J=2Hz, H-2), 8.75 (1H, dd, J=2Hz and J=5Hz, H-6), 8.52-8.01 (3H, complex, H-4', H-7' and H-4), 7.82 (1H, s, H-2'), 7.53-7.22 (3H, complex, H-5, H-5' and H-6') and 2.62 (3H, s, $COCH_3$) ppm.

M.S. m/e (rel. int.%) 264 (M^+, 50), 222 (72) and 144 (100).

(Found: C, 72.7; H, 4.5; N, 10.6. $C_{16}H_{12}N_2O_2$ requires : C, 72.7; H, 4.6; N, 10.6%).

1-Amino-3-(1-acetyl-3-indolylformyl)pyridinium mesitylene sulphonate (135).

The indole (134) (10 g), in dichloromethane (100 ml), was cooled to 0° and O-mesitylsulphonylhyroxylamine (80) (8.2 g, 1 mol equiv.) in dichloromethane (50 ml), added. After several minutes when a dense, white precipitate separated, ether (100 ml) was added and stirring was continued for one hour. The solid was filtered, washed with ether and dried (16.8 g, 92%).

m.p. 198-203°C,

U.V. λ max 230, 261 and 320 nm,

I.R. ν max 1730 (N-Ac) and 1640 ($Ar_2C{=}O$) cm^{-1},

P.M.R. δ (d^6DMSO) 9.25 (1H, s, H-2), 8.84 (1H, d, J=6Hz, H-6), 8.61-8.42 (3H, complex, H-2' and NH_2), 8.34-7.89 (4H, complex, H-4, H-5, H-4' and H-7'), 7.39-7.20 (2H, m, H-5' and H-6'), 6.55 (2H, s, aryl protons of mesitylate anion), 2.75 (3H, s, $NCOCH_3$), 2.50 (6H, s, $2xCH_3$) and 2.1 (3H, s, CH_3) ppm.

Reaction of the salt (135) with acetic anhydride.

A slurry of the salt (135) (20 g) in chloroform (300 ml) was stirred vigorously while acetic anhydride (20 ml) was added. After one hour the reaction was basified with aqueous sodium bicarbonate solution and the organic phase separated, washed with water, dried and evaporated to give a white solid which crystallized from chloroform as needles (10.6 g, 90%).

m.p. 179-181°C,

U.V. λ max 226, 265 and 322 nm,

I.R. ν max 1715 (N-Ac), 1645 ($Ar_2C{=}O$) and 1555 ($\overset{+}{N}$-$\bar{N}$-Ac) cm^{-1},

P.M.R. δ ($CDCl_3$) 9.38 (1H, bs, H-2), 8.71-8.25 (5H, complex, H-4, H-6, H-2', H-4' and H-7'), 7.88 (1H, dd, J=6Hz and J=8Hz, H-5), 7.43 (2H, m, H-5' and H-6'), 2.88 (3H, s, $NCOCH_3$) and 2.05 (3H, s, $\overset{+}{N}$-$\bar{N}COCH_3$) ppm.

M.S. m/e (rel. int.%) 321 (M^+, 27), 306 (23), 278 (24), 264 (56), 238 (17), 222 (65) and 144 (100).

If the reaction is carried out in aqueous ethanol or the basification procedure is not completed quickly indole de-N-acetylation occurs and the mono-acetyl derivative (137) is obtained as pale, yellow florets.

m.p. 241-243°C (dec),

U.V. λ max 215, 240, 270, 328 and 349 nm,

I.R. ν max 3100 (N-H), 1620 ($Ar_2C{=}O$) and 1560 ($\overset{+}{N}\text{-}\bar{N}\text{-}\overset{O}{\overset{\|}{C}}CH_3$) cm^{-1},

P.M.R. δ (d^6DMSO) 12.31 (1H, bs, N-H), 9.12 (1H, s, H-2), 8.85 (1H, d, J=6Hz, H-6), 8.46-8.09 (3H, complex, H-4, H-2' and H-4'), 7.91 (1H, dd, J=6Hz and J=8Hz, H-5), 7.54-7.04 (3H, m, H-5', H-6' and H-7') and 1.95 (1H, s, $\overset{+}{N}\text{-}\bar{N}\text{-}COCH_3$) ppm.

M.S. m/e (rel. int.%) 279 (M^+, 6), 264 (9), 222 (100) and 144 (100).

1-(N-Acetyl-N-methylamino)-3-(1-acetyl-3-indolylformyl) pyridinium iodide (138).

The diacetyl product (136) (10 g) was heated under reflux for one hour with methyl iodide (20 ml) and acetone (50 ml). On cooling the title compound was obtained as a bright yellow solid (12.8 g, 89%).

m.p. 234-236°C (dec),

U.V. λ max 230, 263 and 312 nm,

I.R. ν max 1720 ($N\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$), 1695 ($\overset{+}{N}\text{-}N\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$) and 1645 ($Ar_2C{=}O$) cm^{-1}

P.M.R. δ (d^6DMSO) 10.1 (1H, s, H-2), 9.66 (1H, d, J=6Hz, H-6), 9.35 (1H, d, J=8Hz, H-4), 8.78-8.22 (4H, complex, H-5, H-2', H-4' and H-7'), 7.68-7.47 (2H, m, H-5' and H-6'), 3.93 (3H, s, $N\text{-}CH_3$), 2.82 (3H, s, $N\text{-}COCH_3$) and 2.31 (3H, s, $\overset{+}{N}\text{—}N\text{-}COCH_3$) ppm

M.S. sample not volatile.

(Found: C, 49.4; H, 4.0; N, 9.0. $C_{19}H_{18}N_3IO_3$ requires : C, 49.3; H, 3.9; N, 9.1%).

1-Acetylindol-3-yl 1-(N-acetyl-N-methylamino)-4-cyano-1,4-dihydropyrid-3-yl ketone (139)

A dispersion of the metho salt (138) (2 g), in water (200 ml), was stirred at room temperature while ammonium chloride (0.68 g) and potassium cyanide (0.33 g), in water (25 ml), were added. After one hour dichloromethane (75ml) was introduced and the mixture stirred for a further ten minutes. The aqueous phase was extracted with more dichloromethane (2x50 ml) and the organic phase and extracts combined, washed with water (4x50 ml), dried and evaporated. Removal of the solvent furnished a yellow gum which rapidly turned green. This material was dissolved in a little warm ethanol and allowed to cool whereupon yellow prisms of the title compound separated (0.92 g, 86%).

m.p. 154-155°C (dec.)(MeOH),

U.V. λ max 228, 255, 293, 300 and 340 nm,

I.R. ν max 2230 (C≡N), 1720 (N-Ac), 1690 (N-N-Ac) and 1600 ($Ar_2C{=}O$) cm^{-1},

P.M.R. δ (d^6DMSO) 8.35 (2H, complex, H-4' and H-7'), 7.95 (2H, complex, H-2 and H-2'), 7.36 (2H, m, H-5' and H-6'), 6.61 (1H, m, H-6), 5.21 (1H, m, H-5), 4.75 (1H, m, H-4), 3.15 (3H, 2xs, N-CH_3), 2.72 (3H, s, N-$COCH_3$) and 2.01 (3H, 2xs, N-N-$COCH_3$) ppm.

M.S. In the mass spectrum only ions due to the aromatic nitrile (128) are observed.

(Found: C, 67.4; H, 5.2; N, 17.3. $C_{18}H_{16}N_4O_2$ requires : C, 67.5; H, 5.0; N, 17.5%).

Indol-3-yl 4-cyanopyrid-3-yl ketone (128)

The 1,4-dihydropyridine described in the previous experiment may be converted into the corresponding pyridine by heating gently in organic solvents (pref. ethanol), or by irradiation with ultra-violet light. From dimethyl sulphoxide pale yellow prisms are obtained.

m.p. 256-258°C ($(CH_3)_2SO$),

U.V. λmax 220, 234, 268 and 323 nm,

I.R. νmax 2220 (C≡N) and 1620 ($Ar_2C{=}O$) cm^{-1},

P.M.R. δ(d^6DMSO) 12.22 (1H, bs, N-H), 9.15 (1H, s, H-2), 9.05 (1H, d, J=5Hz, H-6), 8.31 (1H, m, H-4'), 8.15 (1H, s, H-2'), 8.05 (1H, d, J=5Hz, H-5) and 7.71-7.23 (3H, complex, H-5', H-6' and H-7') ppm.

M.S. m/e (rel. int.%). 247 (M^+, 98), 219 (30), 205 (32) and 144 (100).

(Found: C, 72.8; H, 3.8; N, 16.8; $C_{15}H_9N_3O$ requires : C, 72.9; H, 3.7; N, 17.0%).

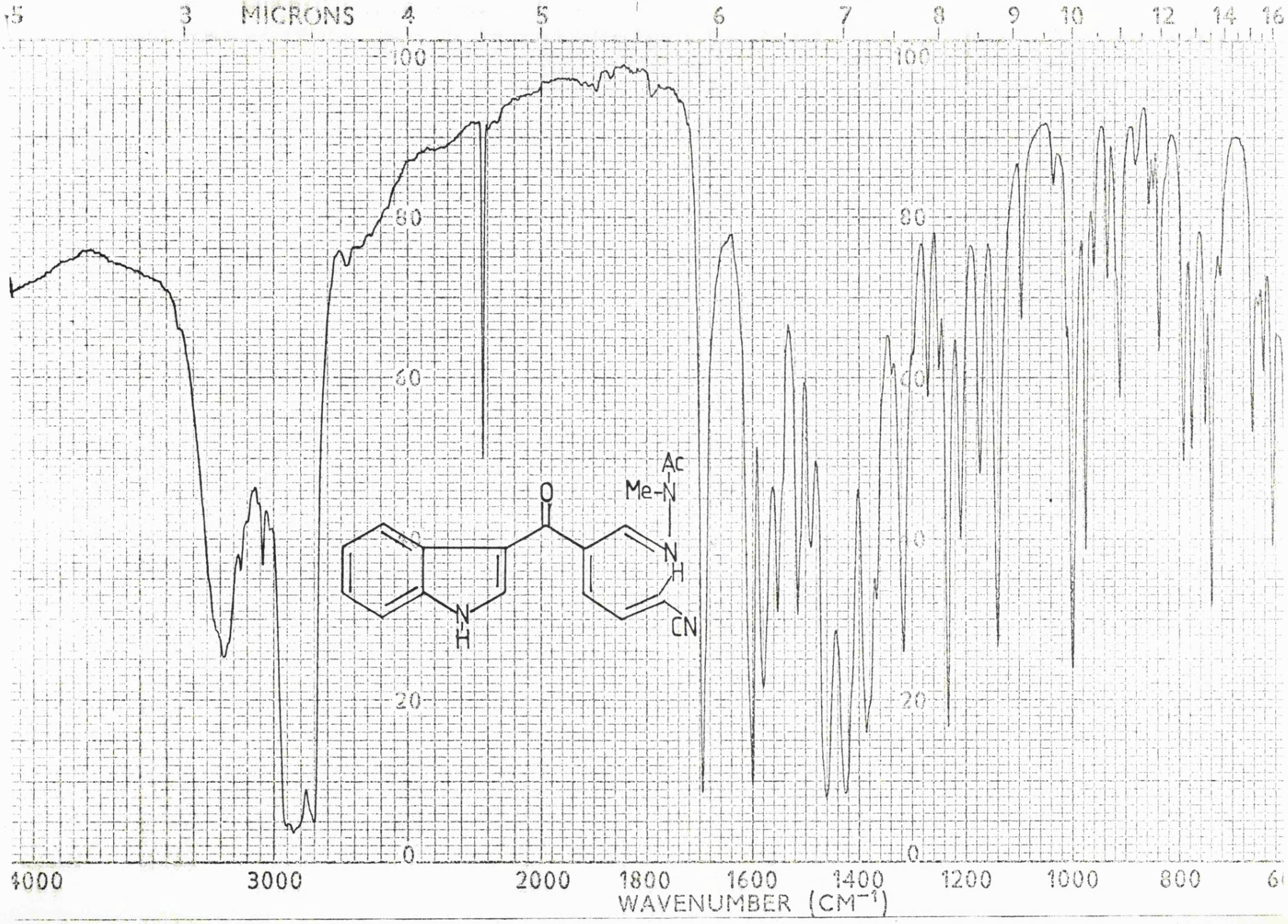
(precision mass measurement. Found: 247.0742 $C_{15}H_9N_3O$ requires : 247.0746).

Indol-3-yl 6-cyanopyrid-3-yl ketone (141)

The metho salt (138) (1.3 g), dispersed in chloroform (100 ml) was stirred vigorously as first ammonium chloride (0.5 g) in water (20 ml) was added and then as potassium cyanide (0.23 g) in water (20 ml) was introduced. After one hour the aqueous phase was separated and extracted with chloroform (3x50 ml). The combined chloroform phases were washed with water (3x30 ml), dried and evaporated to give a yellow foam which was dissolved in methanol (100 ml) and irradiated with ultra-violet light (medium pressure lamp) for two hours. Finally the solution was evaporated to low bulk when yellow prisms separated (0.28 g, 42%).

m.p. 260°C ($(CH_3)_2SO$),

U.V. λmax 217, 235, 270 and 329 nm,


MICRONS
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WAVENUMBER (CM⁻¹)

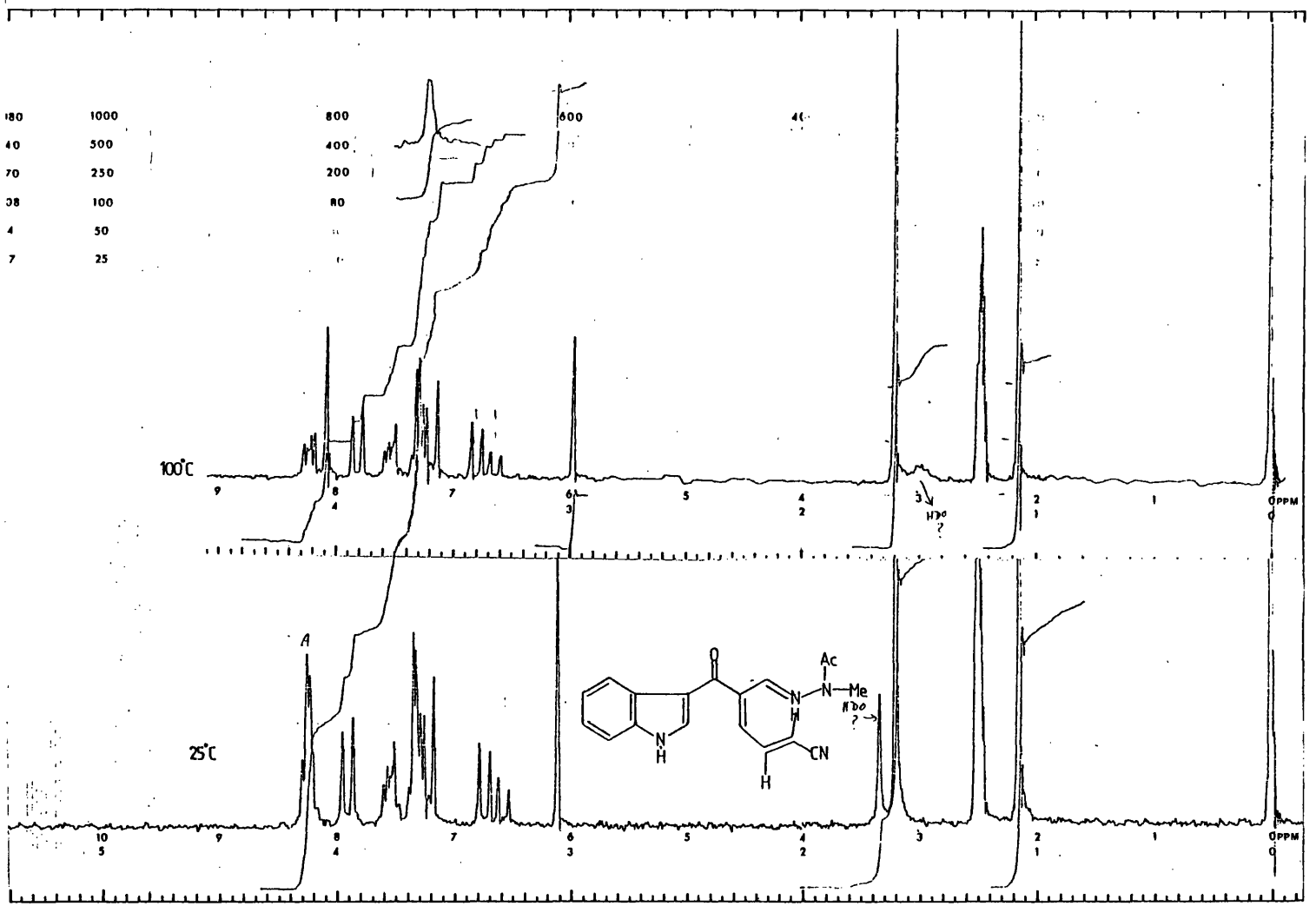

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Chart No. 4H–C

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I.R. ν max. 3200(N-H), 2220(C≡N) and 1620(Ar_2C=O) cm^{-1},

P.M.R. δ (d^6DMSO) 12.25 (1H, bs, N-H), 9.06 (1H, d, J=2Hz, H-2), 8.41-7.82 (4H, complex, H-4, H-5, H-2' and H-4'), 7.40 (1H, m, H-7') and 7.35-7.12 (2H, m, H-5' and H-6') ppm.

M.S. m/e (rel. int.%) 247 (M^+, 96), 219 (25) and 144 (100).

(Found: C, 72.6; H, 3.9; N, 17.1. $C_{15}H_9N_3O$ requires : C, 72.9; H, 3.7; N, 17.0%).

Indol-3-yl 1-(N-acetyl-N-methylaminoimino)-5-cyano-3,4-pentadien-2-yl ketone (145)

When the above reaction was repeated with the contents of the reaction vessel protected from light a pale yellow solid was obtained (yield, 70%).

m.p. 246-249°C(dec.) ($CHCl_3$),

U.V. λ max 212, 245, 263 and 322 nm,

I.R. ν max 3200(N-H), 2220(C≡N), 1700(N-Ac) and 1600(Ar_2C=O) cm^{-1},

P.M.R. δ (d^6DMSO) 12.41 (1H, bs, N-H), 8.31 (1H, m, H-4), 8.25 (1H, s, H-2'), 7.92 (1H, d, J=9Hz, H-3), 7.59 (1H, m, H-7'), 7.38-7.17 (3H, m, H-5, H-5' and H-6'), 6.71 (1H, dd, J=16.5Hz and J=9Hz, H-4), 6.17 (1H, s, H-1),3.21 (3H, s, N-CH_3) and 2.18 (3H, s, N-$COCH_3$) ppm.

M.S. m/e (rel. int.%) 320(M^+, 60), 293 (5), 277 (21), 262 (6), 248 (15) and 144 (100).

(Found: C, 67.6; H, 5.1; N, 17.3. $C_{18}H_{16}N_4O_2$ requires : C, 67.5; H, 5.0; N, 17.5%).

Reaction of indol-3-yl 4-cyanopyrid-3-yl ketone (128) under hydrolytic conditions.

(a) With dilute hydrochloric acid

The nitrile (128) (100 mg) was stirred, vigorously, with 2N hydrochloric acid (10 ml) for one hour. The undissolved solid was filtered and shown to be the pyridinium hydrochloride salt of the starting material. The remaining solution was neutralised with

dilute ammonium hydroxide solution and extracted with chloroform (4 x 15 ml). No material was obtained from the combined organic extracts.

The experiment was next repeated heating under reflux for up to 12 hours but with similar results.

(b) With sulphuric acid

The nitrile (128) (100 mg) was treated with 50% sulphuric acid (10 ml) at room temperature, to give a dark red solution which was warmed, (50°C) with stirring overnight and then poured onto crushed ice (20 g). The mixture was neutralised with dilute ammonia solution and extracted with chloroform (3 x 25 ml). The combined, dried extracts were evaporated affording a pale yellow solid (80 mg, 75%). This material proved to be a mixture of the starting nitrile and the acid (221).

The use of more concentrated acid solutions led to the formation of considerable amounts of tarry material as did vigorous heating.

(c) With dilute sodium hydroxide

The nitrile (128) (100 mg) was heated for one hour with 1N sodium hydroxide solution (10 ml). Very little material dissolved and on work-up only starting material was obtained.

In the next experiment a solution of the nitrile (100 mg) in ethylene glycol (10 ml) was heated under reflux with 30% sodium hydroxide for one hour during which time the initially pale yellow solution darkened and then became almost colourless. The solution was cooled, adjusted to pH4 and washed well with ether (2 x 75 ml). The solution was next made neutral with dilute sodium hydroxide solution and extracted with chloroform (3 x 25 ml). Evaporation of the combined organic extracts yielded a small amount of an orange gum which was vacuum dried. Crystallization attempts were unsuccessful

and TLC analysis suggested the presence of a complex mixture.

(d) With potassium hydroxide

A solution of the nitrile (100 mg), in aqueous methanol (10 ml, 7:3), was heated under reflux for two hours with potassium hydroxide (0.07g, 3 mol equiv.). On cooling the solution was adjusted to pH4 when a white solid separated which was filtered and recrystallized from methanol to give colourless needles of indol-3-yl 4-carboxylpyrid-3-yl ketone (130) (HCl salt) (96 mgs, 79%).

m.p. 254°C (dec.),

U.V. λmax 214, 256 and 328 nm,

I.R. νmax 3300-3100 (O-H and N-H), 2800-2600(O-H), 1700 (acid C=O) and 1610(bridge C=O) cm^{-1},

P.M.R. δ (d^6DMSO) 12.22 (2H, 2xbd, NH, $\overset{+}{N}H$), 8.91 (1H, d, J=5Hz, H-6), 8.76 (1H, s, H-2), 8.49-8.03 (4H, complex,H-5, H-2', H-4' and $CO_2\underline{H}$) and 7.71-7.05 (3H, complex, H-5', H-6' and H-7') ppm.

M.S. m/e (rel. int.%). 266(M^+, 92), 222 (63), 144 (100) and 69 (100).

(Found: C, 60.0; H, 3.7; N, 10.3. $C_{15}H_{11}N_2O_3Cl$ requires: C, 59.7; H, 3.6; N, 10.5%).

(Precision mass measurement. Found: 266.0692 $C_{15}H_{10}N_2O_3$ requires : 266.0690).

When the 2-cyano analogue (141) was treated in a similar fashion both the corresponding acid (m.p. 251°C) and the acid amide were obtained. The amide, isolated from alkaline solution, has,

m.p. 255°C (dec.),

U.V. λ max 224, 268 and 322 nm,

I.R. ν max 3430, 3390(CON-H), 3200(N-H), 1695(amide I), 1605(bridge C=O), 1595 and 1590 (amide II) cm^{-1},

P.M.R. δ (d^6DMSO) 12.21 (1H, bs, N-H), 9.1 (1H, s, H-2), 8.46-8.12 (6H, complex, H-4, H-5, H-2', H-4' and NH_2) and 7.21-7.53 (3H, m, H-5', H-6' and H-7') ppm.

M.S. m/e (rel. int.%) 265 (M^+, 82), 247 (25) and 144 (100).

(Found: C, 67.7; H, 4.1; N, 15.7. $C_{15}H_{11}N_3O_2$ requires : C, 67.9; H, 4.2; N, 15.9%)

Attempted reaction of indol-3-yl 4-cyanopyrid-3-yl ketone (128) with methyl lithium.

The nitrile (128) (100 mg) in dry THF was added dropwise to a stirred solution of methyl lithium, in anhydrous ether at -10°C, under an inert atmosphere. Stirring was continued for 30 minutes when water (2 ml) followed by saturated ammonium chloride solution (5 ml) was added. The organic solvents were evaporated and the residue extracted thoroughly with chloroform (4 x 25 ml). The combined organic extracts were washed with brine, dried and evaporated to yield a pale yellow solid which was shown (TLC, pmr, ir) to be starting material.

When the experiment was carried out at 0° or when a larger excess of methyl lithium was employed similar results were obtained.

Reduction of indol-3-yl 4-cyanopyrid-3-yl ketone (128) with sodium borohydride.

A solution of the nitrile (128) (100 mg) in ethanol (15 ml) at room temperature was treated, portion-wise, with sodium borohydride until a constant ultra-violet trace was obtained. Excess reducing agent was destroyed by the careful addition of acetone when the solution was evaporated to dryness and the residue partitioned between chloroform (30 ml) and water (30 ml). The

organic layer was separated, washed with brine, dried and evaporated to yield a light brown oil which could not be induced to crystallize but showed only one spot on TLC.

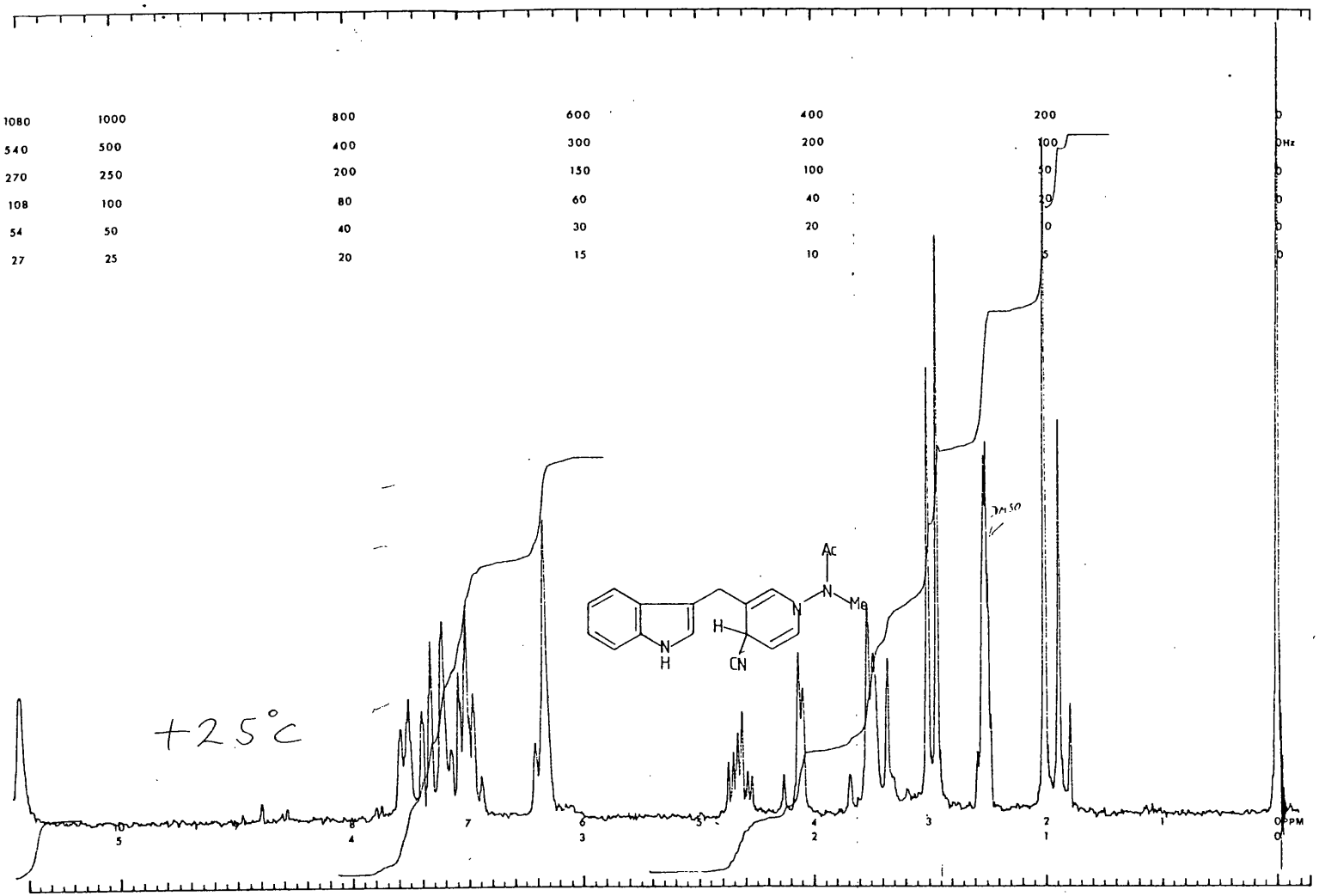
U.V. λ max 221 and 275 nm,

I.R. ν max 3260(O-H), 3160(N-H), 2225(C≡N), 1600 and 1595 (Ar) cm^{-1},

M.S. m/e (rel. int.%) 249 (M^+, 10) and 222(100).

This material was treated with dilute hydrochloric acid without effect while the use of concentrated acid or alkali led to the recovery of small amounts of black tars which were not characterized.

When reaction with methyl lithium was attempted, followed by warming with 20% acetic acid, a black intractible tar was obtained once again.



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Indol-3-yl 3-pyridyl methane (127)

(a) Sodium borohydride reduction

The ketone (126) (6.0 g), in boiling ethanol (100 ml), was treated, portionwise, with sodium borohydride until a constant ultra-violet trace was obtained. The solution was cooled and excess reducing agent destroyed by the addition of water (10 ml). The solvents were evaporated and the residue partitioned between brine (20 ml) and chloroform (100 ml). The organic layer was separated, dried and evaporated to give an orange gum which was triturated with ether to give the title compound as colourless cubes (2.7 g, 48%).

(b) Wolff-Kishner reduction

The ketone (126) (6.0 g) was heated with potassium hydroxide (9.2 g), hydrazine hydrate (9.5 ml) and diethylene glycol (5 ml) for six hours under an inert atmosphere. The orange solution was cooled and poured onto cracked ice (100 g) when a yellow solid separated. The solid was filtered and recrystallized from chloroform (4.3 g, 75%).

m.p. 157°C (lit. 154-156°,[91] lit.[28] 157-158°),

U.V. λ max 235, 270, 284 and 292 nm,

I.R. ν max 3140 (N-H) cm^{-1},

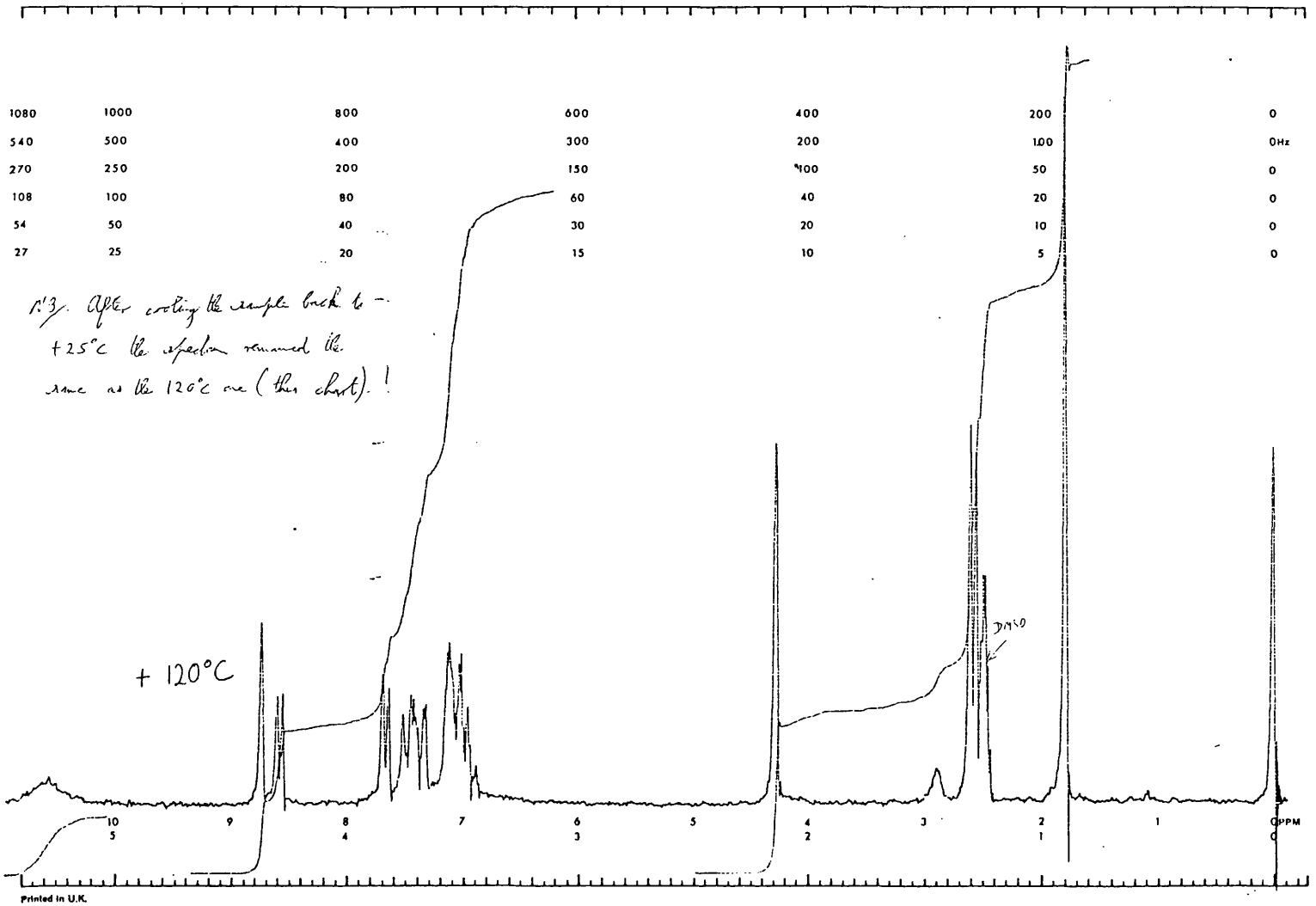
P.M.R. δ (d^6DMSO) 10.94 (1H, bs, N-H), 8.56 (1H, d, J=2Hz, H-2), 8.34 (1H, dd, J=2Hz and J=6Hz, H-6), 7.60 (1H, dt, J=2Hz and J=6Hz, H-4), 7.42-6.82 (6H, complex, H-5, H-2', H-4', H-5', H-6' and H-7') and 4.12 (2H, s, CH_2) ppm.

M.S. m/e (rel. int. %) 208 (M^+, 42) and 92 (100).

(Found: C, 80.4; H, 5.7; N, 13.4. Calc. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5%).

Indol-3-yl 4-cyanopyrid-3-yl methane (132)

The picolyl derivative (127) (3 g) in dichloromethane (150 ml) was cooled to 0°C and treated with MSH (80) (3.2 g) in the same solvent (25 ml). After stirring for one hour the pale brown oil



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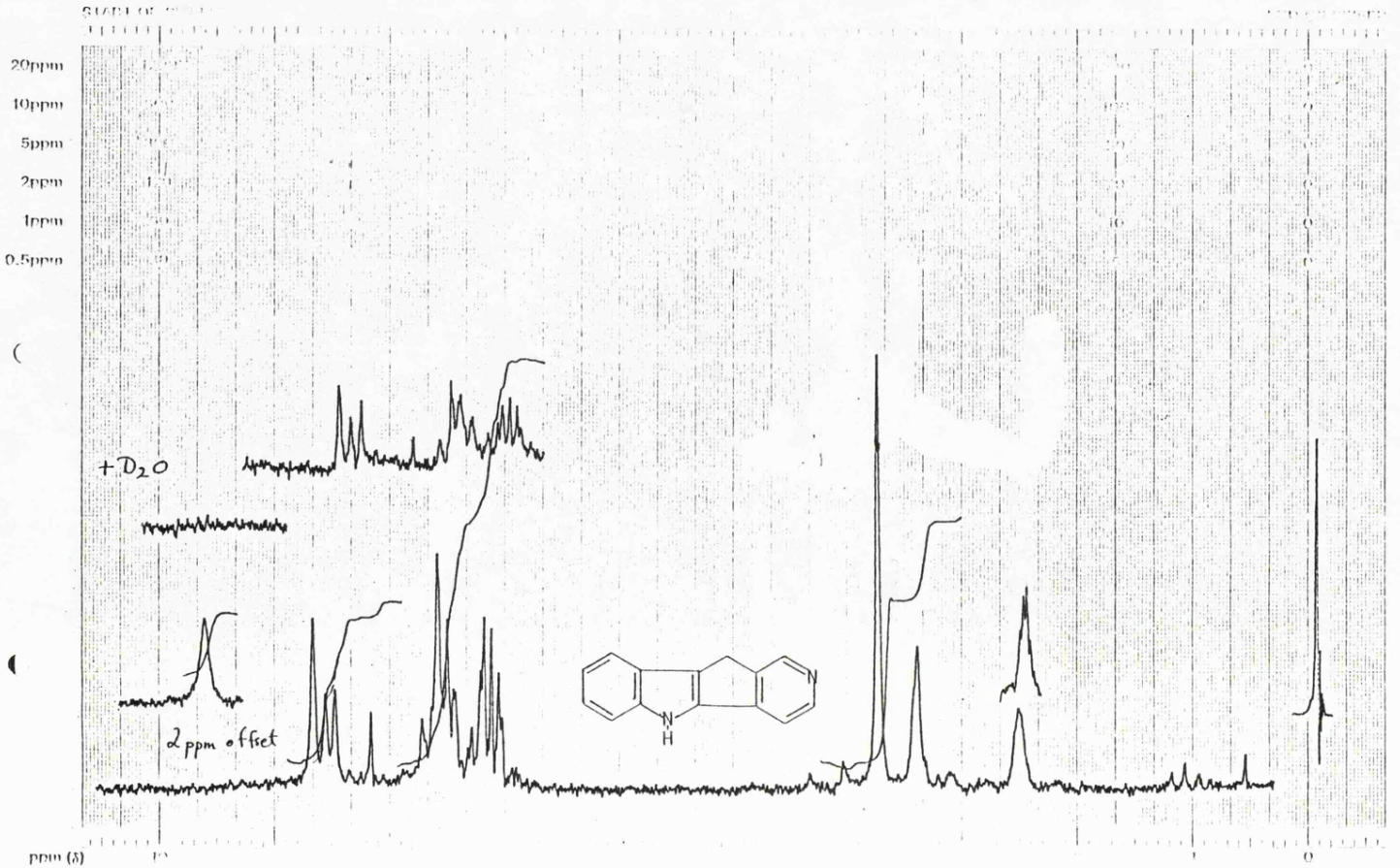
which had separated was collected and washed with ether (5.9 g, 96%), (δ ($CDCl_3$/d^6DMSO) 12.21 (1H, bs, N-H), 8.72 (1H, s, H-2), 8.60 (1H, d, J=6Hz, H-6), 8.23-7.85 (4H, complex, H-2', H-4 and NH_2) 7.50-6.91 (5H, complex, H-5, H-4', H-5', H-6' and H-7'), 6.75 (2H, s, aryl protons of mesitylate anion), 4.22 (2H, s,-CH_2-), 2.52 (6H, s, 2xCH_3) and 2.18 (3H, s, CH_3) ppm.)

The oil (157) (5.8 g), in 50% aqueous ethanol (50 ml), was stirred with acetic anhydride (10 ml) for one hour when sodium bicarbonate solution was added until the mixture was just basic. Evaporation to low bulk followed by extraction with chloroform afforded a brown oil (158) which was heated with methyl iodide (20 ml) in boiling acetone (30 ml) for one hour. The yellow solution was cooled and evaporated to give a yellow solid (5.2 g, 61% from (157)).

This metho salt (159) (5.0 g) was dissolved in water (250 ml), containing ammonium chloride (1.2 g),and treated with a solution of potassium cyanide (.75 g) in water (10 ml). After 90 minutes the mixture was extracted with chloroform and the organic phases combined, washed with water (3 x 50 ml), dried and evaporated to yield a pale brown foam. A little ethanol was added and the solution allowed to stand whereupon crystals of indol-3-yl 1-(N-acetyl-N-methylamino)-4-cyano-1,4-dihydropyrid-3-yl methane (173) separated (1.9 g, 56%). This product,which has m.p. 100°C,displays νmax 3280 (N-H),2235 (C≡N), 1690 (N-N-CO-CH_3), 1615 (C=C) and 1600 (Ar) cm^{-1}, δ ($CDCl_3$) 8.51 (1H, bs, N-H), 7.68-6.98 (5H, complex, H-2', H-4', H-5', H-6' and H-7'), 6.00 (1H, m, H-6), 5.95 (1H, 2xbs, H-2), 4.67 (1H, m, H-5), 4.08 (1H, 2xbd, H-4), 3.63 (2H, s, -CH_2-), 3.03 (3H, 2xs, N-CH_3) and 2.06 (3H, 2 xs, N-CO-CH_3) ppm.

When the dihydropyridine (173) was dissolved in ethanol and heated,or irradiated with ultra-violet light,evaporation of the solution to low bulk gave, on standing, colourless prisms of indol-3-yl



DMSO

1901

4-cyanopyrid-3-yl methane (132) (1.5 g, 44% from (127)).

m.p. 145°C,

U.V. λmax 228, 282 and 291 nm,

I.R. ν max 3150(N-H) and 2220 (C≡N) cm^{-1},

P.M.R. δ (d^6DMSO) 10.51 (1H, bs, N-H), 8.78 (1H, s, H-2), 8.59 (1H, d, J=6Hz, H-6), 7.77 (1H, d, J=6Hz, H-5), 7.58-7.32 (2H, m, H-4' and H-7'), 7.18 (1H, d, J=1Hz, H-2'), 7.12-6.85 (2H, m, H-5' and H-6') and 4.25 (2H, s, $-CH_2-$) ppm.

M.S. m/e (rel. int.%) 233 (M^+, 91), 208 (33) and 130 (100).

(Found: C, 77.3; H, 4.7; N, 18.0. $C_{15}H_{11}N_3$ requires : C, 77.2; H, 4.7; N, 18.0%).

10H-Indolo(3,2-b)-2-azaindene (160).

The nitrile (132) (0.2 g) was heated in boiling 2N hydrochloric acid (25 ml) for one hour during which time the initially colourless solution turned dark red. Basification with dilute ammonium hydroxide and extraction with chloroform afforded a pale yellow solid (0.17 g, 93%).

m.p. 225°C (dec.)

U.V. λ max 225, 228, 250, 256, 335 and 346 nm,

I.R. ν max 3400(N-H) and 1600 (Ar) cm^{-1},

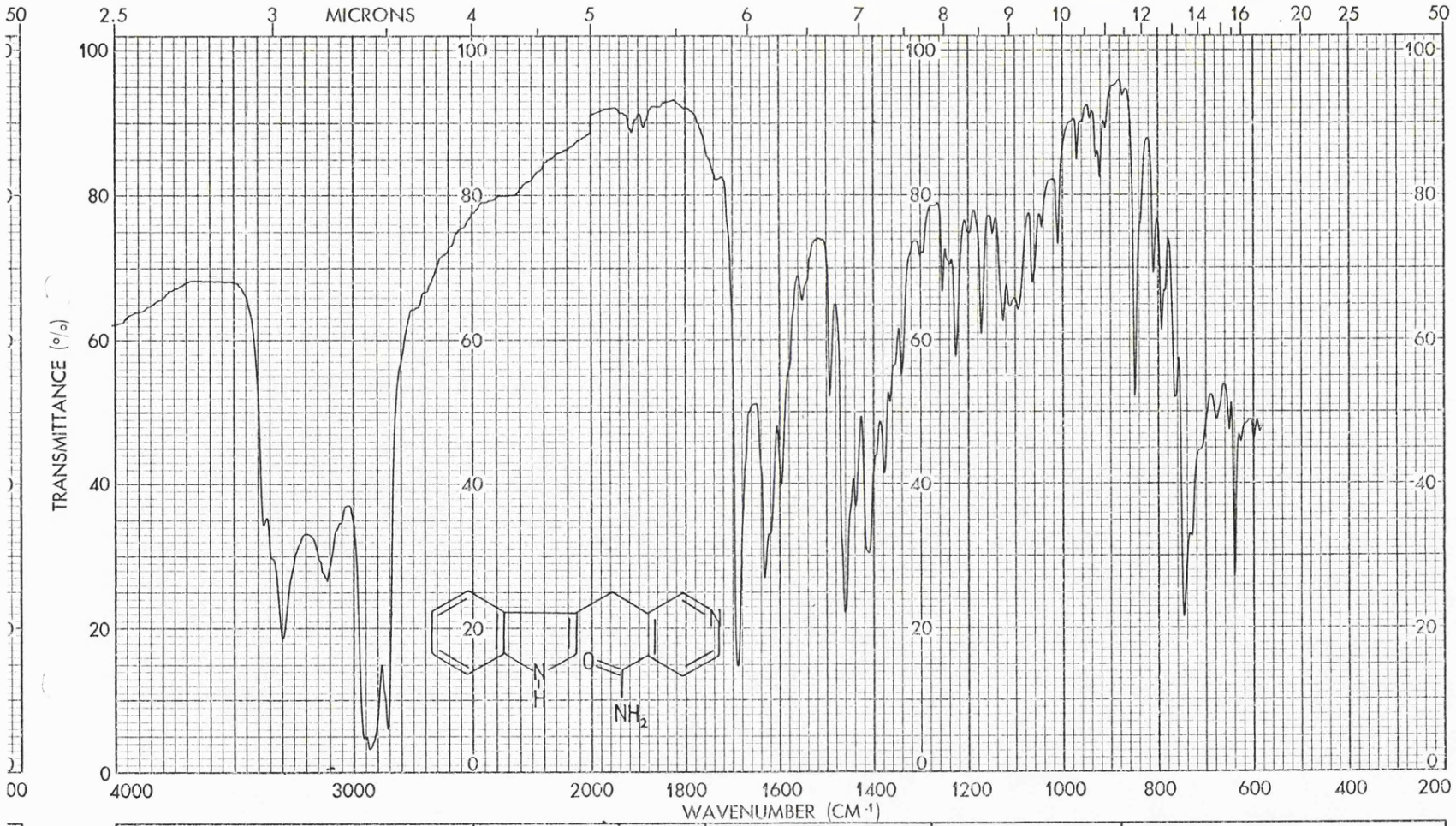
P.M.R. δ (d^6DMSO) 11.6 (1H, bs, N-H), 8.75 (1H, s, H-1), 8.60 (1H, d, J=5Hz, H-3), 7.72-7.39 (3H, complex, H-4, H-6 and H-9), 7.32-7.01 (2H, m, H-7 and H-8) 3.79 (2H, s, H_2-10) ppm.

M.S. m/e (rel. int.%) 206 (M^+, 100) and 178 (7).

(Found: C, 81.4; H, 5.0; N, 13.8. $C_{14}H_{10}N_2$ requires : C, 81.5; H, 4.9; N, 13.6%).

The elemental analysis was carried out upon a small sample which was crystallized from ethyl acetate. The hydrochloride salt, obtained as bright yellow needles from ethanol (m.p. > 310°,

+ D2O
1ppm offset
(215)
δ (ppm)
10
8
6
4
2
0



SAMPLE	SOLVENT Nujol	SCAN 3 mics	SINGLE B.	REMARKS
	CONC.	SLIT	T.D. SPEED.	
	CELL PATH	OPERATOR	ORD. EXP.	
	REFERENCE	DATE	T. CONST	
ORIGIN		PART No. 5102-1000	REF. No	

darkens above 250°C) displays δ(d^6DMSO) 12.20 (1H, bs, N-H), 8.82 (1H, s, H-1), 8.75 (1H, d, J=5Hz, H-3), 7.99 (1H, d, J=5Hz, H-4), 7.65-7.01 (4H, m, H-6, H-7, H-8 and H-9) and 3.81 (2H, s, H_2-10) ppm, (Found: C, 69.3, H, 4.5; N, 11.4. $C_{14}H_{11}N_2Cl$ requires : C, 69.3; H, 4.5; N, 11.6%).

Indol-3-yl 4-carboxamidopyrid-3-yl methane (215)

The nitrile (132) (0.35 g), in water (5 ml) and methanol (5 ml), was heated under reflux for two hours with potassium hydroxide (0.25g, 3 mol equiv.). During this period the initially yellow solution became almost colourless and on cooling a white solid separated. Filtration and recrystallisation from methanol afforded colourless prisms (0.32 g, 83%).

m.p. 194°C.

U.V. λmax 228, 274 and 260 nm,

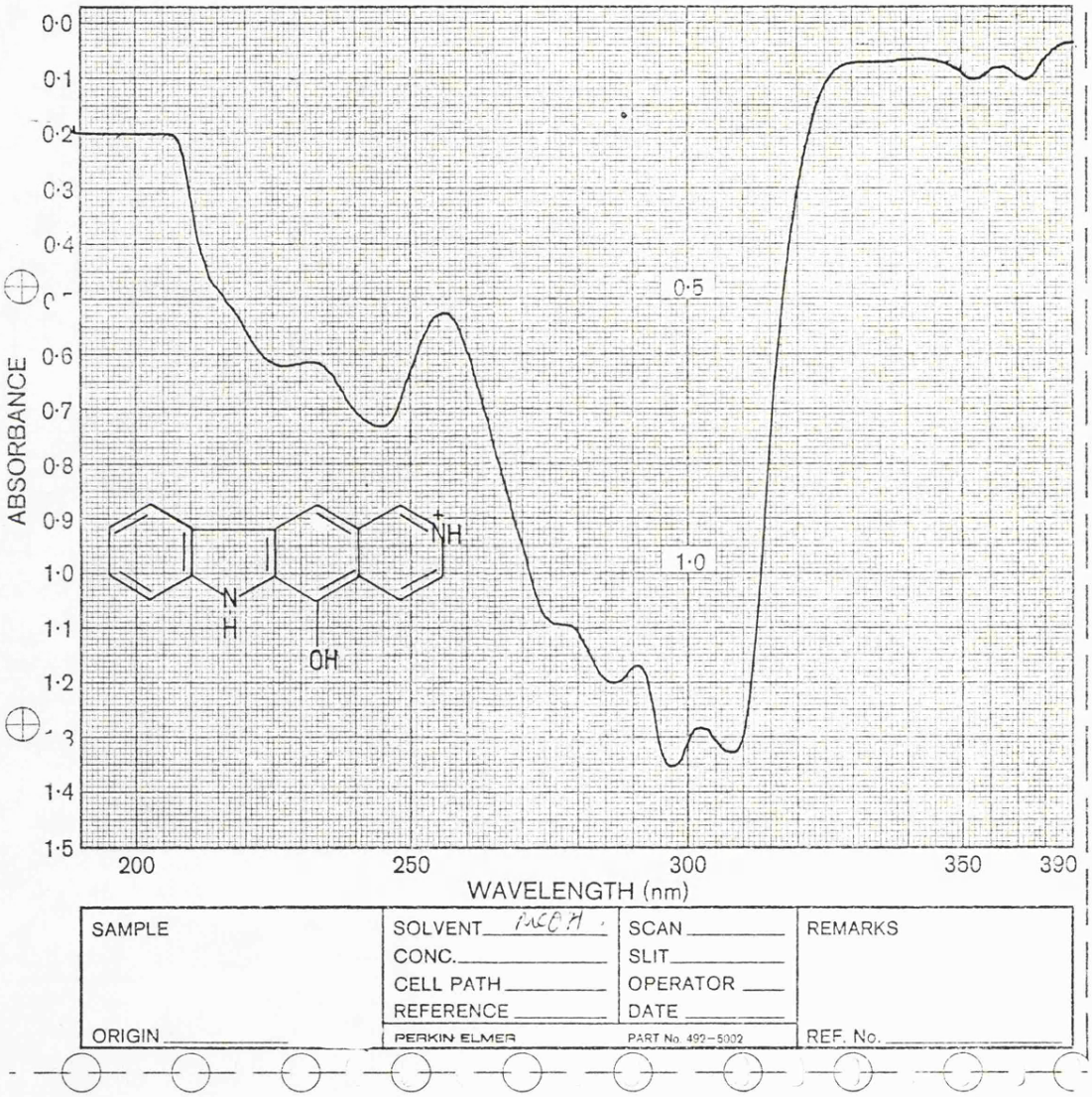
I.R. ν max 3380, 3350, 3330 (CON-H), 3120 (N-H), 1690 (C=O) and 1630 (amide II) cm^{-1},

P.M.R. δ ($(CD_3)_2CO$) 10.62 (1H, bs, NH), 8.54 (1H, s, H-2), 8.45 (1H, d, J=5Hz, H-6), 7.78 (2H, bs, NH_2), 7.54-6.80 (6H, m, H-5, H-2', H-4', H-5', H-6', and H-7') and 4.31 (2H, s, CH2) ppm.

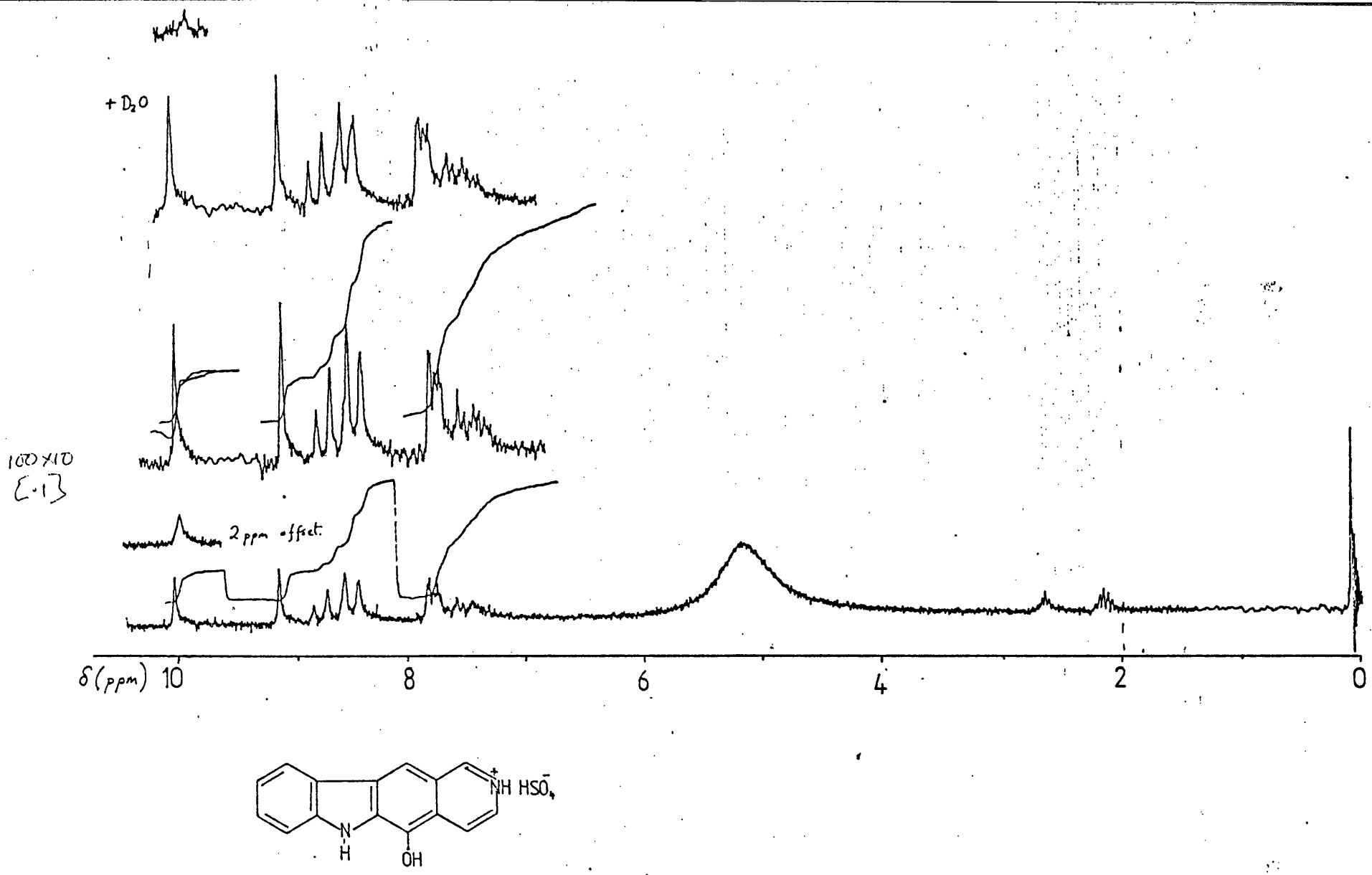
M.S. m/e (rel. int.%). 251 (M^+, 72), 235 (40) and 206 (100).

(Found: C, 71.5; H, 5.3; N, 16.7. $C_{15}H_{13}N_3O$ requires : C, 71.7; H, 5.2; N, 16.7%).

A solution of the amide (215) (100 mg) in water (3.2 ml) and sulphuric acid (0.4 ml) was heated under reflux for 90 minutes when the solution was cooled. The yellow solid that separated was collected by filtration and recrystallised from methanol to give yellow needles. This material is believed to be 5-hydroxy-11-demethylellipticinium hydrosulphate and has,



SAMPLE	SOLVENT MeOH	SCAN	REMARKS
	CONC.	SLIT	
	CELL PATH	OPERATOR	
	REFERENCE	DATE	
ORIGIN	PERKIN ELMER	PART No. 492–5002	REF. No.


+ D2O
100 X 10
[-1]
2 ppm offset
δ (ppm) 10
8
6
4
2
0

NH HSO4
N
H
OH

m.p. decomposes rapidly above 270°C,

U.V. λ max 214, 226, 245, 275, 286, 297, 308, 352 and 362 nm,

I.R. ν max 3350-3150, 1640 and 1610 cm^{-1},

P.M.R. δ (d^6DMSO/d^6ACETONE) 12.00 (1H, bs, N-H), 10.08 (1H, s, H-1), 9.15 (1H, s, H-11), 8.79 (1H, d, J=7Hz, H-3), 8.54 (2H, m, H-4 and OH) and 7.92-7.31 (4H, m, H-7, H-8, H-9 and H-10) ppm.

M.S. sample not volatile

(Found: C, 53.9; H, 3.6; N, 8.1: $C_{15}H_{12}N_2O_5S$ requires C, 54.2; H, 3.6; N, 8.4%).

The free ellipticine (which decomposes in solution over a period of several hours) has,

U.V. λ max 225, 244, 266, 277 and 295 nm,

M.S. m/e (rel. int.%) 234 (M^+, 100).

Attempts to obtain a crystalline sample of this material were unsuccessful as were efforts aimed at preparing an acetylated derivative.

5,6-Methylenedioxyindol-3-yl 3-pyridyl ketone (179).

The title compound was obtained from the reaction of 5,6-methylenedioxyindolyl magnesium bromide with nicotinoyl chloride using the same procedure as that employed for the preparation of indol-3-yl 3-pyridyl ketone (126), the yield of colourless prisms, after recrystallisation from ethanol, was 13%.

m.p. 219°C,

U.V. λ max 233, 262 and 301 nm,

I.R. ν max 3220(N-H), 1600(Ar) and 940(C-O-C) cm^{-1},

P.M.R. δ (d^6DMSO) 11.68 (1H, bs, NH) 8.88 (1H, d, J=1.5Hz, H-2), 8.72 (1H, dd, J=5Hz and J=1.5Hz, H-6), 8.02 (1H, dt, J=8Hz and J=1.5Hz, H-4), 7.68 (1H, s, H-4'), 7.61 (1H, d, J=2Hz, H-2'), 7.47 (1H, dd, J=8Hz and J=5Hz, H-5), 6.96 (1H, s, H-7') and 5.99 (2H, s, CH_2) ppm.

M.S. m/e (rel. int.%) 266 (M^+, 72) and 188 (100).

(Found: C, 67.5; H, 3.9; N, 10.5. $C_{15}H_{10}N_2O_3$ requires : C, 67.7; H, 3.8; N, 10.5%).

Reduction of (179) with sodium borohydride

The ketone (179) (1 g) in boiling ethanol (25 ml) was treated, portionwise, with sodium borohydride until a constant ultra-violet trace was obtained. The mixture was cooled and excess reducing agent destroyed by the addition of acetone (10 ml). Evaporation to dryness, followed by partitioning between chloroform and water ultimately afforded a brown gum (0.9 g, 95%).

U.V. λ max 235 nm,

I.R. ν max 3200 (N-H)and 1595(Ar) cm^{-1},

M.S. m/e (rel. int.%) 252 (M^+, 81) and 174 (100).

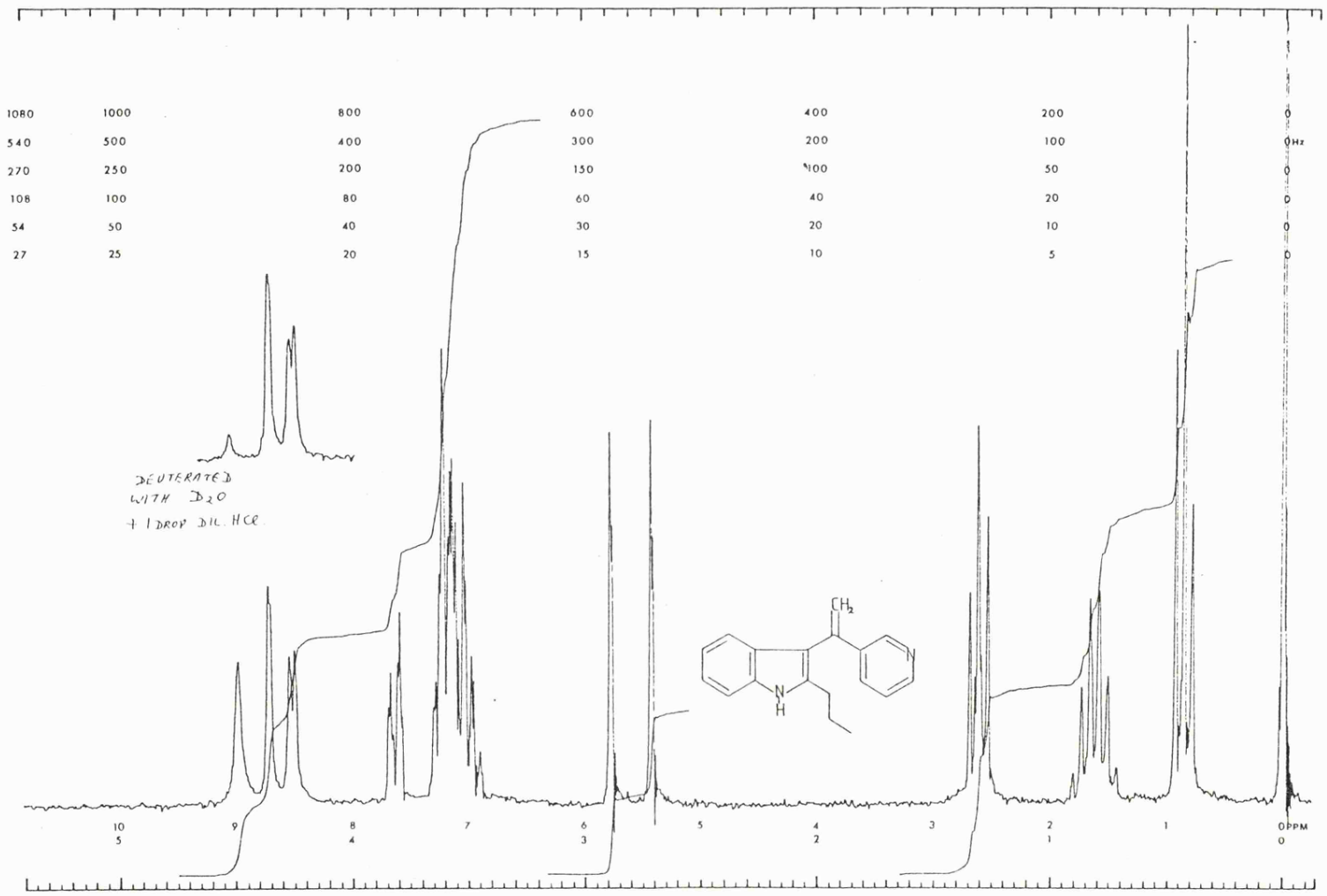
This material was subjected to the usual sequence of reactions with MSH, acetic anhydride and methyl iodide to give a small amount of a brown gum. No satisfactory spectral data was obtained from this substance.

Reaction between indol-3-yl 4-cyanopyrid-3-yl methane (132) and hydrogen chloride

The 4-cyanopyridine (132) (200 mg) in dry T.H.F. (25 ml) containing anhydrous zinc chloride (50 mg) was cooled to -20°C and saturated with hydrogen chloride. After one hour the red solid which had separated was collected by filtration, washed with ether and dried. This material, which has m.p. 270-280°C displays λmax 220, 245, 283, 320, 333 and 353 nm and νmax 3290, 3250, 3230, 3100, 1660, 1640 and 1605 cm^{-1}.

This red solid (.1 g) was dissolved in water (5 ml) and warmed where upon a bright yellow fluorescence soon developed. After several minutes the solution began to turn green and, on the addition of base, darkened while the fluorescence was much reduced. After a further period of warming the green solution became orange in colour. Extraction with organic solvents at any of the above stages gave only intractible residues which defied attempts to induce crystallization and which we were unable to characterise fully.

A sample of the red solid was treated with dilute sodium bicarbonate solution and extracted with chloroform to give, on evaporation, a dark, amorphous solid which has m.p. 268-279°C, λmax 295, νmax 3450-3250 and 1600 cm^{-1}, δ ($CDCl_3$) 11.4 (1H, bs), 8.1-7.9 (2H, m), 7.6-7.2 (3H, m), 7.1-7.9 (3H, m) and 6.2 (2H, bs) ppm.



Printed in U.K.

Chart No. 4H–C

Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

2-n-Propylindole (186).

Butyryl o-toluidine (185) (20 g) (from the reaction of o-toluidine with butyric anhydride) was added to sodium amide (13.1 g, 3 mol equiv.) under an inert atmosphere and the mixture stirred with ether (10 ml) while the temperature was raised to 240°C over a period of 30 minutes. Nitrogen was evolved at temperatures above 200°C and the mass solidified. On cooling ethanol (20 ml) was carefully added and the mixture then dissolved in an ethanol/water solution. Extraction with ether gave an oil which was distilled at 168° at 0.6 mm Hg to give a colourless oil which crystallized on cooling (14.1 g, 78%).

m.p. 34 - 35°C,

I.R. ν max 3400 (N-H), 2960 (C-H), 1620 and 1580 (Ar) cm^{-1},

P.M.R. δ ($CDCl_3$) 7.59-6.96 (5H, complex, H-4, H-5, H-6, H-7 and NH), 6.12 (1H, s, H-3), 2.53 (2H, q, J=7Hz, $C\underline{H}_2$) 1.65 (2H, m, $CH_2C\underline{H}_2CH_3$) and 0.94 (3H, t, J=7Hz, $CH_2C\underline{H}_3$) ppm.

2-n-Propyl-3-(1-(3-pyridyl)vinyl)indole (187)

2-n-Propylindole (186) (10 g) and 3-acetylpyridine (7.6 g), in methanol (100 ml), previously saturated with hydrogen bromide, were heated at reflux for three hours. The solution was then cooled, poured onto ice and basified with ammonium hydroxide. The product was extracted into dichloromethane and, after drying, the solvent was removed to give a white solid which was recrystallized from ethanol (13.4 g, 81%).

m.p. 132-133°C.

U.V. λ max 239, 249 and 284 nm,

I.R. ν max 3120 (N-H) and 1620 ($C=CH_2$) cm^{-1},

P.M.R. δ ($CDCl_3$) 8.95 (1H, bs, NH), 8.75 (1H, d, J=1Hz, H-2), 8.45 (1H, dd, J=1Hz and J=6Hz, H-6), 7.63 (1H, dt, J=1Hz and J=8Hz, H-4), 7.25-6.85 (5H, complex, H-5, H-4', H-5', H-6' and H-7'), 5.75 (1H, d, J=2Hz, vinyl proton), 5.38 (1H,

d, J=2Hz, vinyl proton), 2.58 (2H, t, J=7Hz, Ar-CH_2-), 1.62 (2H, sextet, CH_2-CH_2-CH_3) and 0.85 (3H, t, J=7Hz, -CH_2-CH_3) ppm.

M.S. m/e (rel. int.%) 262 (M^+, 100), 219 (12) and 185 (60).

(Found: C, 82.4; H, 6.8; N, 10.7. $C_{18}H_{18}N_2$ requires : C, 82.4; H, 6.9; N, 10.7%).

1-(n-Butyl)-3-(1-(2-n-propyl-3-indolyl)vinyl)pyridinium bromide (188)

The vinylindole (187) (5 g) and n-butyl bromide (10 g) were heated together, under reflux, for five hours. The excess alkyl halide was decanted leaving a brown gum which was dried under high vacuum. (7.4 g, 97%).

U.V. λmax 236, 265 and 292 nm,

I.R. νmax 3100(N-H), 1615 (C=$\overset{+}{N}$) and 1605 (C=CH_2) cm^{-1},

P.M.R. δ($CDCl_3$) 10.12 (1H, bs, NH), 9.28 (1H, d, J=6Hz, H-6), 9.02 (1H, s, H-2), 8.24 (1H, m, H-4), 7.92 (1H, m, H-5), 7.61 (1H, m, H-4'), 7.07-6.63 (3H, m, H-5', H-6' and H-7'), 6.28 (1H, s, vinyl proton), 5.58 (1H, s, vinyl proton), 2.73 (2H, m, $\overset{+}{N}$-CH_2), 1.85 (4H, m, 2xCH_2), 1.22 (4H, m, 2xCH_2) and 0.91 (6H, m, 2xCH_3) ppm.

5-Ethylellipticine (189)

The pyridinium salt (188) (5 g) in a round-bottomed flask, fitted with an inverted splash-head, was carefully heated over a luminous Bunsen flame for five minutes. The dark mass was allowed to cool, finely ground and extracted with chloroform (5 x 100 ml). The organic extracts were 'charcoaled' and the dark residue, left after evaporation of the solvent, was chromatographed on silica. Elution with petrol/chloroform (4:1) yielded a yellow solid which was sublimed in vacuo. The sublimate was recrystallized from ethanol to give needles (0.05 g, 1.5%).

m.p. 295°C (sublimes),

U.V. λmax 240, 266, 277, 294 and 298 nm,

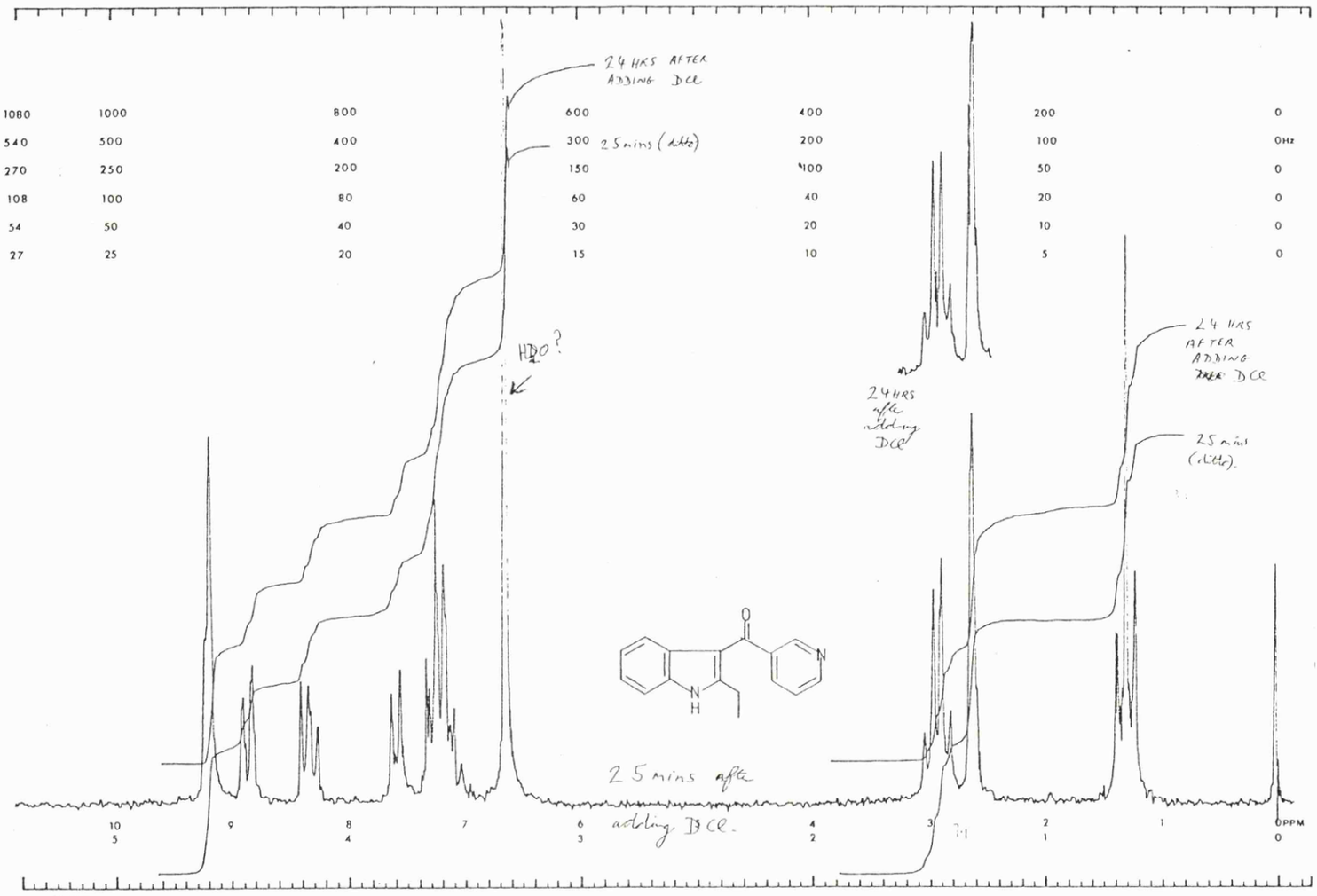


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Chart No. 4H–C

Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

I.R. ν max 3120(N-H), 1610(Ar) and 1605(Ar) cm^{-1},

P.M.R. δ (d^6DMSO) 12.20 (1H, s, NH), 9.92 (1H, s, H-1), 8.41-8.12 (3H, complex, H-3, H-4 and H-10), 7.48-7.00 (3H, complex, H-7, H-8 and H-9), 3.40 (2H, q, J=9Hz, $C\underline{H}_2CH_3$), 3.35 (3H, s, CH_3) and 1.32 (3H, t, J=9Hz, $CH_2C\underline{H}_3$) ppm.

M.S. m/e (rel. int.%) 260 (M^+, 74) 245 (100), 231 (6).

(Found: C, 83.1; H, 6.3; N, 10.6. $C_{18}H_{16}N_2$ requires : C, 83.0; H, 6.2; N, 10.8%).

2-Ethylindol-3-yl 3-pyridyl ketone (196)

2-Ethylindole (40.6 g) (from a Madelung reaction on proprionyl o-toluidine), in dry ether (50 ml) was added to an ethereal solution of ethylmagnesium bromide (0.28M) at 0°C and stirred for 30 minutes. The resulting suspension of Grignard reagent was added, dropwise, to a stirred solution of nicotinoyl chloride (0.27M) in dry benzene at -10°C. After four hours the mixture was allowed to warm to room temperature and left overnight. Saturated ammonium chloride solution (30 ml) was then added and the product extracted with dichloromethane (3 x60 ml). Evaporation of the combined, dry extracts furnished the ketone as an orange solid which was recrystallized from methanol (22 g, 31%).

m.p. 199-201°C.

U.V. λmax 238, 265 and 325 nm,

I.R. νmax 3160 (N-H), 1595 (C=O) and 1585(Ar) cm^{-1},

P.M.R. δ(d^6DMSO) 11.95 (1H, bs, NH), 8.79 (2H, m, H-2 and H-6), 8.02 (1H, dt, J=1.5Hz and J=8Hz, H-4), 7.62-7.30 (2H, m, H-5 and H-4'), 7.28-7.00 (3H, m, H-5', H-6' and H-7'), 2.85 (2H, q, J=8Hz, $C\underline{H}_2$) and 1.20 (3H, t, J=8Hz, $C\underline{H}_3$) ppm.

M.S. m/e (rel. int.%) 250(M^+, 81), 221 (43) and 172 (100).

(Found: C, 76.6; H, 5.5; N, 11.4. $C_{16}H_{14}N_2O$ requires : C, 76.8; H, 5.6; N, 11.2 %).

1-(n-Butyl)-3-(2-ethyl-3-indolylformyl)pyridinium bromide (198).

The pyridinium salt (198) was obtained as an amorphous, brown solid after treatment of the ketone (196) with boiling n-butyl bromide. (Yield 91%).

U.V. λmax 235, 245, 266 and 330 nm,

I.R. ν max 3150 (N-H), 1615(C=$\overset{+}{N}$) and 1605 (C=O) cm^{-1},

P.M.R. δ (d^6DMSO) 12.13 (1H, bs, N-H), 9.41 (2H, m, H-2 and H-6), 8.85 (1H, m, H-4), 8.38 (1H, m, H-4'), 7.64 (1H, m, H-5), 7.46-7.16 (3H, m, H-6', H-7' and H-8'), 2.95 (2H, q, J=8Hz, CH_2) and 1.3 (3H, t, J=8Hz, CH_3) ppm.

Pyrolysis of the salt (198)

Pyrolysis of (198) was carried out using the same procedure as for (188) to give a dark residue which by TLC was shown to be a highly complex mixture. Several highly fluorescent components were present but despite several chromatographic purification attempts no characterisation of any of these components was achieved.

Other attempts to effect cyclisation of (198)

(I) Reaction with base

The salt (198) was treated with sodium ethoxide (1:1 and excess) for periods of up to one week at room temperature but only starting materials were isolated.

When the mixture was heated to reflux or when stronger base was employed similar results were obtained.

(II) Photochemical reactions

Both the salt (198) and the pyridine analogue (196) were subjected to photolysis using medium and high pressure lamps in ethanolic solution and in the presence of base. In every case unchanged starting material was obtained.

5-n-Butyl-11-demethylellipticine (203)

Indol-3-yl 4-cyanopyrid-3-yl methane (132) (125 mg) in anhydrous diethyl ether (30 ml) was added, dropwise, to a solution of n-butyl lithium (3 mol equiv.) in hexane at -10°C. After stirring for 30 minutes, iced water (5 ml) was added followed by 10% ammonium chloride in water. The organic phase was separated, dried and evaporated to yield a gum which was heated with 20% aqueous acetic acid (5 ml) on a steam bath for 45 minutes. The solution was then cooled, basified with potassium carbonate and extracted with chloroform (4 x 20 ml). The combined, dried extracts were evaporated to low bulk when yellow needles separated (127 mg, 87%).

m.p. 299-301°C (dec, darkens above 270°C),

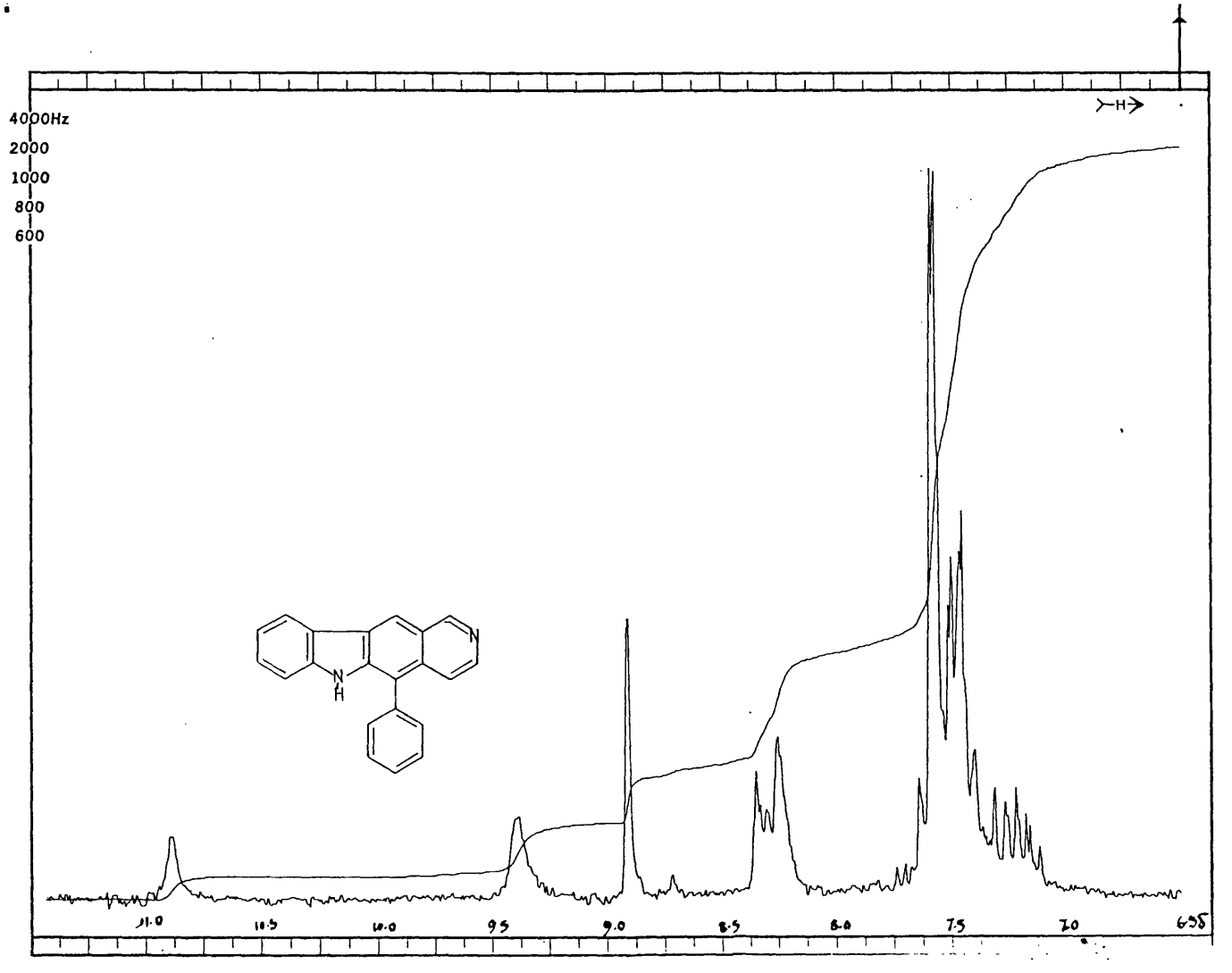
U.V. λ max 225, 240, 265, 274, 285, 295 and 298 nm,

I.R. ν max 3140(N-H), 1610(Ar) and 1600(Ar) cm^{-1},

P.M.R. δ (CF_3CO_2H) 9.36 (1H, d, J=7Hz, H-1), 8.78 (1H, s, H-11), 8.48-8.13 (3H, m, H-3, H-4 and H-10), 7.79-7.34 (3H, m, H-7, H-8 and H-9), 3.42 (2H, t, J=8Hz, $-CH_2CH_2CH_2CH_3$), 1.82 (4H, m, $CH_2CH_2CH_2CH_3$) and 1.19 (3H, t, J=8Hz, CH_3), ppm.

M.S. m/e (rel. int.%) 274 (M^+, 37) and 231 (100).

(Found: C, 83.0; H, 6.4; N, 10.1. $C_{19}H_{18}N_2$ requires : C, 83.2; H, 6.6; N, 10.2%).


4000Hz
2000
1000
800
600
H
N
H
N
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5δ

5-n-Butylellipticine (202)

The title compound was prepared from the nitrile (82,R=Ac) using a similar procedure to that described in the previous experiment. Yield 78%, yellow needles from chloroform.

m.p. 285-287°C (sublimes),

U.V. λ max 240, 277, 287 and 295 nm,

I.R. ν max 3150(N-H), 1605(Ar) and 1600(Ar) cm^{-1},

P.M.R. δ (CF_3CO_2H) 9.59 (1H, d, J=7Hz, H-1), 8.48 (3H, complex, H-3, H-4 and H-10), 7.66-7.25 (3H, complex, H-7, H-8 and H-9), 3.41 (2H, t, J=8Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.30 (3H, s, CH_3), 1.78 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$) and 1.11 (3H, t, J=8Hz, $-CH_2C\underline{H}_3$) ppm,

M.S. m/e (rel. int.%) 288 (M^+, 50), 245 (100).

(Found: C, 83.2; H, 6.9; N, 9.6. $C_{20}H_{20}N_2$ requires : C, 83.3; H, 7.0; N, 9.7%).

5-Phenyl-11-demethylellipticine (207)

The title compound was from the nitrile (132) by the action of phenyl lithium using a similar procedure to that described above. The product crystallized from ethanol as pale yellow platelets (20%).

m.p. 289-290°C (rapid heating), product sublimes 280-285°C,

U.V. λ max 208, 226, 265, 276, 285, 293 nm,

I.R. ν max 3150(N-H) 1605(Ar) and 1600(Ar) cm^{-1},

P.M.R. δ (d^6DMSO) 10.92 (1H, bs, NH), 9.41 (1H, bs, H-1), 8.92 (1H, s, H-11), 8.40-8.13 (2H, m, H-3 and H-4) and 7.63-7.09 (9H, complex, remaining protons) ppm,

M.S. m/e (rel. int.%) 294 (M^+,100) and 147 (12).

(Found: C, 85.6; H, 7.8; N, 9.3. $C_{21}H_{14}N_2$ requires : C, 85.7; H, 7.8; N, 9.5%).

(Precision mass measurement. Found: 294.1161 $C_{21}H_{14}N_2$ requires: 294.1157).

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